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THE NATION'S FOOD

A SURVEY OF SCIENTIFIC DATA

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Some thirty authors have contributed to this book. Many of them are well known for their original contributions in the fields of biochemistry or food technology. They come from laboratories at academic centres, at government research institutions and at food factories. The book thus represents a piece of scientific collaboration by experts selected without any consideration other than their ability to assemble information and give it accurate expression. The authors have brought together all the knowledge at present available about the composition of the foods, and therefore the diets, of the British people. This has involved a detailed examination of seven main foods or groups of foods and the recording of innumerable data giving their chemical compositions.

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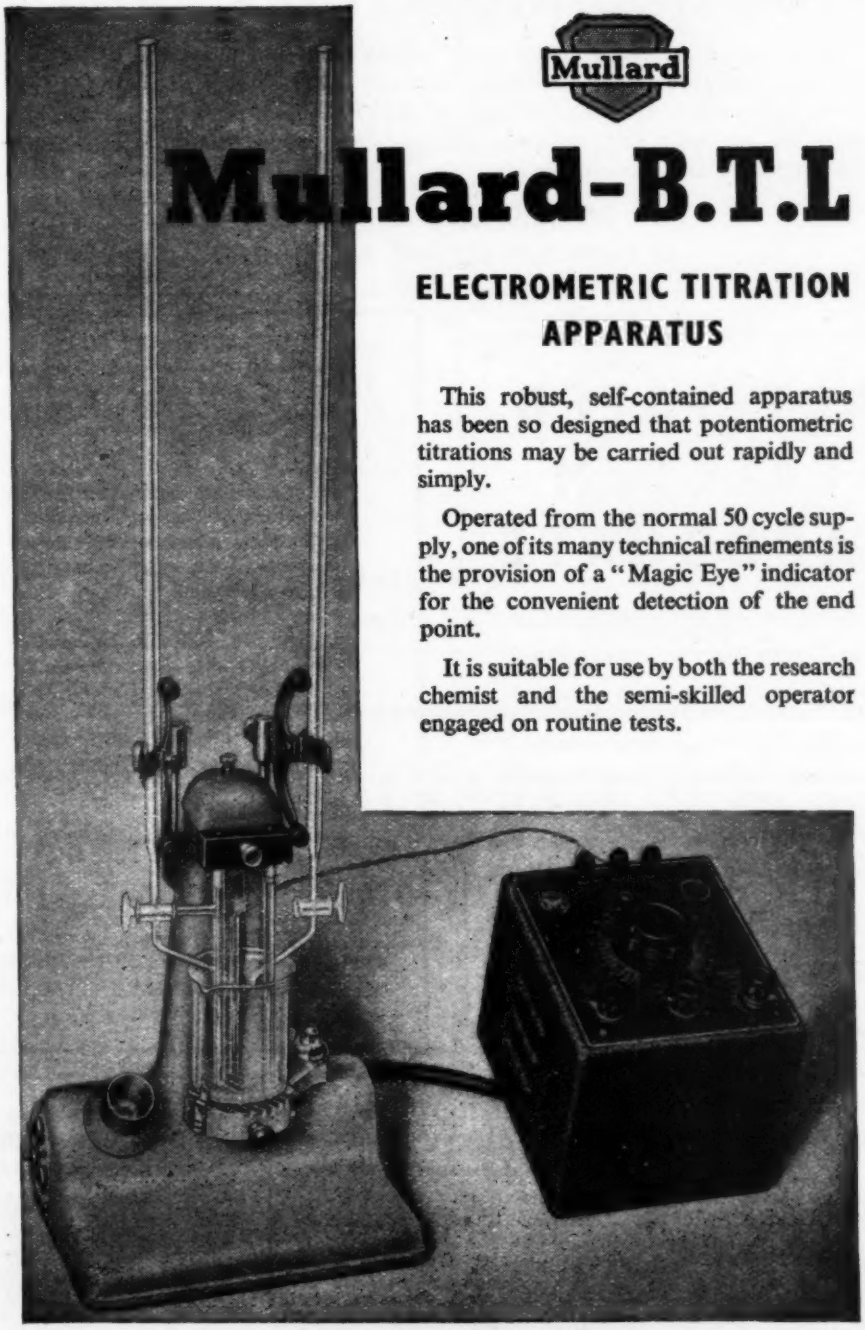

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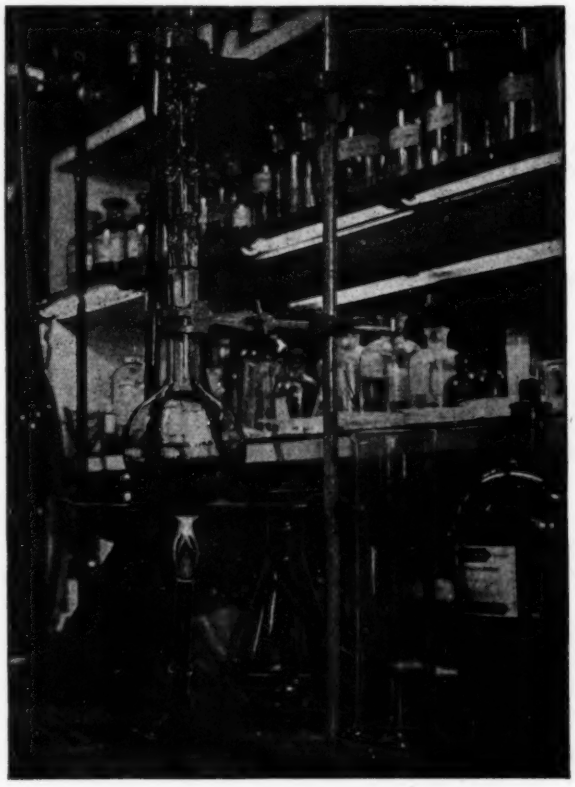

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1·4 g. The combined products were recrystallised from 5% alcoholic hydrochloric acid to give the *hydrochloride* in yellow needles, m. p. 151—152° (Found: N, 4·7; Cl, 27·9. $C_{12}H_{10}O_2NCl,HCl$ requires N, 5·1; Cl, 26·1%). The free *6-methoxy-8-quinolyl chloromethyl ketone*, obtained by addition of cold 2N-sodium hydroxide to an aqueous solution of the hydrochloride, crystallised from light petroleum (b. p. 80—100°) in slightly pink felted needles, m. p. 120° when heated rapidly; slow heating caused decomposition without melting at 116° (Found: Cl, 14·5. $C_{12}H_{10}O_2NCl$ requires Cl, 15·1%).

When the above reaction was carried out at 5—10° the product was a dark oil which slowly crystallised as the hydrochloride from alcoholic hydrogen chloride. The free base crystallised from alcohol (some decomp.) in large yellow rhombs, m. p. 80°. The *hydrochloride* crystallised from alcohol in yellow needles which fell to a powder when dried in a vacuum, and which sintered at 168°, began to decompose at 175° (with evolution of gas), and melted at 180—200° (Found: N, 5·3. $C_{13}H_{13}O_2N,HCl$ requires N, 5·3%).

6-Methoxy-8-quinolyl Diethylaminomethyl Ketone.—The above chloromethyl ketone hydrochloride (11 g.), diethylamine (16·5 g.), and anhydrous benzene (100 c.c.) were heated under nitrogen at 40° for 3 hours. After removal of diethylamine hydrochloride the benzene was evaporated at 30° under reduced pressure. The residue was thoroughly extracted with boiling light petroleum (b. p. 40—60°). Removal of the solvent under reduced pressure gave a deep red oil (5·3 g.), b. p. 150—160°/0·1 mm. (some decomp.). The *dipicrate* crystallised from acetone in yellow prisms, m. p. 142° (Found: C, 45·8; H, 3·6; N, 15·35. $C_{16}H_{20}O_2N_2,2C_6H_3O_7N_3$ requires C, 46·0; H, 3·6; N, 15·3%).

6-Methoxy-8-quinolyl Di-n-Butylaminomethyl Ketone.—A mixture of the chloromethyl ketone hydrochloride (1 g.), di-*n*-butylamine (1·4 g.), and benzene (10 c.c.) at 25° for 16 hours gave 0·9 g. of a deep red oil, b. p. 186—190°/0·5 mm. (some decomp.). The *dipicrate* crystallised from acetone in yellow prisms, m. p. 141° (decomp.) (Found: N, 14·2. $C_{20}H_{28}O_2N_2,2C_6H_3O_7N_3$ requires N, 14·2%).

Reduction of 6-Methoxy-8-quinolyl Diethylaminomethyl Ketone.—The ketone (2·75 g.) in 0·5 methanolic N-hydrochloric acid (20 c.c.) was hydrogenated at 25° under atmospheric pressure in presence of Adams's catalyst (0·2 g.); 330 c.c. (theory, 290 c.c.) of hydrogen were absorbed in 0·5 hour. After filtration, the solution was evaporated to 5 c.c., diluted with water (10 c.c.), basified with 2N-ammonia, and filtered. The residue was washed and the filtrate extracted with ether. The combined extract, after being dried (K_2CO_3), yielded a red oil (2·2 g.). Extraction of this with boiling light petroleum (b. p. 40—60°) gave a red oil (1·75 g.). The *styphnate* crystallised from acetone in red needles, m. p. 164° (Found: C, 51·0, 51·2; H, 5·4, 5·6; N, 13·55. $C_{16}H_{22}O_2N_2,C_6H_3O_8N_3$ requires C, 51·0; H, 4·85; N, 13·5%).

The authors thank Mr. G. Newbery, B.Sc., F.R.I.C., for advice and criticism, Mr. S. Bance, B.Sc., A.R.I.C., for the semi-micro-analyses, and the Directors of Messrs. May and Baker Ltd. for permission to publish these results.

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[*Received, March 6th*, 1947.]

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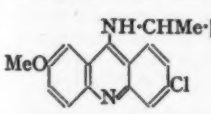
24. *A Resolution of Mepacrine* [*2-Chloro-5-(δ-diethylamino-α-methylbutyl)amino-7-methoxyacridine*].

By B. R. BROWN and D. LL. HAMMICK.

Mepacrine has been resolved in the form of its salt with *d*-4 : 6 : 4′ : 6′-tetranitrodiphenic acid. We obtain $[\alpha]_D$ − 197° and + 205° for the free base in ethyl alcohol, and $[\alpha]_D$ −379° and + 388° for the hydrochloride in water. Previous values are $[\alpha]_D$ − 194·5° and + 197° (Tschelincev and Osetrova, *J. Gen. Chem. Russia*, 1940, **18**, 1978) for the free base in ethyl alcohol, and $[\alpha]_D$ − 357° and + 358·6° (*loc. cit.*) and − 334° and + 355° (Bacher, Buhs, Hetrick, Reiss, and Trenner, *J. Amer. Chem. Soc.*, 1947, **69**, 1534) for the hydrochloride in water.

MEPACRINE [2-chloro-5-(δ-diethylamino-α-methylbutyl)amino-7-methoxyacridine (I)] has been resolved by Tschelincev and Osetrova (*loc. cit.*) by the use of what is described as " αα′-bromocamphorsulphonic acid ".



(I.)

We have failed to repeat the resolution by means of any of the available bromocamphorsulphonic acids, possibly owing to our inability to prevent the separation of the mepacrine salts in non-crystalline forms. Bacher, Buhs, Hetrick, Reiss, and Trenner (*loc. cit.*) appear to have overcome this difficulty by the admixture of small quantities of 2-ethoxyethanol (cellosolve) with the solvent (acetone), and have made a complete resolution with *d*-α-bromocamphor-π-sulphonic acid. We have now effected a complete resolution, already reported in brief (*Nature*, 1947, **159**, 612), into optical antimers having a slightly higher specific rotation than those hitherto reported, by means of *d*-4 : 6 : 4′ : 6′-tetranitrodiphenic acid.

EXPERIMENTAL.

dl-4 : 6 : 4′ : 6′-Tetranitrodiphenic acid was prepared by the nitration of a mixture of 4 : 6′- and 4 : 4′-dinitrodiphenic acids (Christie and Kenner, *J.*, 1922, 619); colourless needles from nitromethane, m. p. 291—293° (decomp.).

The racemic acid was resolved by the method of Christie and Kenner (*loc. cit.*) through the brucine

salt. The *d*-acid was obtained from the less soluble brucine salt as colourless needles, m. p. 227—228°, $[\alpha]_D^{18°}$ + 126° ± 4° (*c*, 0·8 in N/10-sodium hydroxide). Christie and Kenner (*loc. cit.*) give m. p. 226—227°, $[\alpha]_D$ + 115° (aqueous solution of sodium salt).

l-*Mepacrine* d-*Tetranitrodiphenate*.—Boiling solutions of the *d*-acid (1·0 g.) and mepacrine monohydrate (2·0 g.) in ethyl alcohol (20 and 30 c.c. respectively) were mixed. In the course of 4 weeks at room temperature, the initial sticky precipitate changed into clusters of thick yellow transparent needles. This *product* (1·5 g.) was separated, well washed with alcohol and dried in a vacuum at 20°; m. p. 170° (decomp.), $[\alpha]_D^{14°}$ − 162° ± 5° (*c*, 0·08 in 10·4N-acetic acid) (Found: C, 52·9; H, 5·0; N, 11·5; Cl, 4·1. $C_{14}H_8O_{12}N_4,C_{23}H_{30}ON_3Cl,H_2O$ requires C, 52·9; H, 4·5; N, 11·7; Cl, 4·2%).

The preparation of this salt in a state of lower optical purity, but in a much shorter time, was achieved as follows: a mixture of the *d*-acid (0·5 g.), mepacrine monohydrate (1·0 g.), and dioxan (2 c.c.) was warmed until a homogeneous yellow syrup resulted. This was diluted with boiling ethyl alcohol (15 c.c.) and kept for 2 days at room temperature. Small yellow transparent crystals (0·55 g.) separated, $[\alpha]_D^{16°}$ − 126° ± 4° (*c*, 0·32 in 10·4N-acetic acid).

l-*Mepacrine Dihydrochloride*.—*l*-Mepacrine *d*-tetranitrodiphenate (2·2 g.) was decomposed by means of aqueous sodium hydroxide, and the liberated mepacrine was taken up in ether. After removal of the ether, the free base was dissolved in ethyl alcohol (20 c.c.) and the solution made acid to Congo-red by the addition of a 15% solution of hydrogen chloride in alcohol. After 24 hours the crystalline *dl*-mepacrine dihydrochloride was separated and the mother liquor treated with an equal volume of ether. Pure *l*-mepacrine dihydrochloride (0·6 g.) separated in the form of very small yellow needles, m. p. 244—245° (decomp.), $[\alpha]_D^{14°}$ − 379° ± 6° (*c*, 0·1 in water). Tschelincev and Osetrova (*loc. cit.*) give m. p. 243° (decomp.), $[\alpha]_D$ − 357°. Bacher, Buhs, Hetrick, Reiss, and Trenner (*loc. cit.*) obtained $[\alpha]_D^{25°}$ − 334° (*c*, 2 in water).

l-Mepacrine obtained from the hydrochloride, was a yellow transparent oil, $[\alpha]_D^{17°}$ − 197° ± 5° (*c*, 0·4 in ethyl alcohol). Tschelincev and Osetrova (*loc. cit.*) report $[\alpha]_D$ − 194·5° in ethyl alcohol.

d-*Mepacrine Dihydrochloride*.—The alcoholic mother liquor from the initial crystallisation of *l*-mepacrine *d*-tetranitrodiphenate was evaporated, and the residual mixture of partially resolved mepacrine and *d*-acid treated with sodium hydroxide solution and the base isolated by means of ether. Pure *d*-mepacrine dihydrochloride (0·15 g.) was isolated as described for the *l*-salt; small yellow needles, m. p. 244—245° (decomp.), $[\alpha]_D^{10°}$ + 388° ± 7° (*c*, 0·2 in water). Tchelincev and Osetrova (*loc. cit.*) record m. p. 243° (decomp.), $[\alpha]_D$ + 358·6°. Bacher, Buhs, Hetrick, Reiss, and Trenner (*loc. cit.*) obtained $[\alpha]_D^{23°}$ + 355° (*c*, 2 in water).

d-Mepacrine was a yellow transparent oil, $[\alpha]_D^{10°}$ + 205° ± 5° (*c*, 0·2 in ethyl alcohol). Tschelincev and Osetrova (*loc. cit.*) give $[\alpha]_D$ + 197° in ethyl alcohol.

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25. *The Kinetics of Aromatic Halogen Substitution. Part IV. The 1-Halogenonaphthalenes and Related Compounds.*

By P. B. D. DE LA MARE and P. W. ROBERTSON.

Naphthalene, its 1-halogeno-derivatives, and certain other compounds, in the concentration region M/5—M/20 in acetic acid, are brominated by a mechanism resulting in reaction orders of up to 4. Alterations in the conditions have effects similar to those found for the third-order brominations in more dilute solution, but the high orders appear to be more persistent in the former case. Both brominations and chlorinations are acid-catalysed. Rate comparisons are recorded for the chlorination of PhF, PhCl, PhBr, and of 1-fluoro-, -chloro-, and -bromo-naphthalene; and for the bromination under various conditions of naphthalene and its 1-halogeno-derivatives (R′X), the reactivities of which, per replaceable hydrogen atom, are in the order R′F > R′H > R′I > R′Cl > R′Br. The kinetics of bromination are consistent with the participation of a mechanism involving Br_4 molecules. The rate ratios can be interpreted in terms of the electron-withdrawing inductive effect and the electron-donating mesomeric effect; the presence of a polarisability effect contributing to the rate differences in the order I > Br > Cl > F provides a reasonable explanation of the differences between the results for bromination and those recorded by other workers for nitration.

(a) *Kinetics of Bromine Substitution*.—In Part I (*J.*, 1943, 276), bromine substitution of relatively rapidly reacting substances (such as anisole, mesitylene, acetanilide) in dilute (*ca.* M/40) acetic acid solution was shown to proceed by third-order kinetics. Two possible mechanisms were proposed:

$$AH + Br_2 \rightleftarrows AHBr_2; \quad AHBr_2 + Br_2 \longrightarrow ABr + HBr + Br_2 \quad . \quad . \quad . \quad (a)$$

$$Br_2 + Br_2 \rightleftarrows Br_4; \quad AH + Br_4 \longrightarrow ABr + HBr + Br_2 \quad . \quad . \quad . \quad . \quad (b)$$

At high temperatures, great dilutions, or in aqueous acetic acid, the incursion of a bimolecular mechanism caused the kinetics to change towards second order.

More slowly reacting compounds examined in the concentration region M/10 were found to give kinetic orders greater than 3. This at first surprising result was shown not to be associated

with disturbances due to the formation of HBr_3, which is less active than Br_2 in substitution, but may catalyse the substitution process. Such high orders considerably restrict the range of dilution over which the reaction can be accurately followed; but it was shown that, as for the third-order substitutions, the kinetic order was reduced by dilution or by high temperature.

Reaction orders approximating to $n = 4{\cdot}0$ have now been established for *o*- and *m*-xylene (in acetic acid containing 1% of water, M/5—M/10); and for naphthalene and its 1-halogen-derivatives (in acetic acid, M/5—M/10). Similarly, *N*-methylacetanilide gave in acetic acid $n = 3{\cdot}6$ (M/5—M/10); $n = 3{\cdot}3$ (M/10—M/20). The high reaction orders do not, therefore, appear to be peculiar to a particular type of compound, but are general, and are consistent with the participation in the reaction of associated bromine molecules, Br_4. There is no evidence, other than kinetic, as far as we are aware, for the existence of Br_4 in acetic acid solution, but a very small concentration might account for the observations, as the polar form $Br^{\oplus}Br_3^{\ominus}$ should be an active electrophilic reagent. The lowering of the reaction order on dilution is due to the gradual dominance of the concomitant third-order reaction; if only the fourth-order and the second-order reactions were present, the rate would fall off more rapidly as the concentration was decreased. Similarly, the results of Part I established the existence of a distinct third-order mechanism in the bromination of acetanilide and other compounds.

The contribution of the aromatic compound to the high reaction order is scarcely greater than one, as shown by the following results (in acetic acid at 25°): naphthalene + bromine, reactants M/5, k_2 (l. g.-mol.$^{-1}$ min.$^{-1}$, $x = 10\%$ reaction) 0·116; M/10, 0·029; naphthalene M/5, bromine M/10, 0·029. Similarly for 1-bromonaphthalene, reactants at the same concentrations, $k_2 = 0{\cdot}0025$, 0·00062, 0·00066, respectively. Bromine substitution, like electrophilic bromine addition, therefore, proceeds by a composite mechanism, the full rate expression being:

$$-\mathrm{d}[Br_2]/\mathrm{d}t = k_4[A][Br_2]^3 + k_3[A][Br_2]^2 + k_2[A][Br_2]$$

(cf. Swedlund and Robertson, *J.*, 1947, 630).

In acetic acid containing 1% of water, the rate of bromination of naphthalene and of *m*-xylene is increased by a factor of *ca.* 1·5, with no detectable change in reaction order. Further dilution with water reduces the order; thus for 1-chloronaphthalene in acetic acid containing 17% of water, the rate is increased some 40 times as compared with the rate in pure acetic acid, and the order (M/5—M/10) is reduced to 3·6. The high reaction order persists in methyl alcohol (in which solvent, bromine addition to stilbene is bimolecular, as shown by Bartlett and Tarbell, *J. Amer. Chem. Soc.*, 1936, **58**, 466). In this solvent at 25°, the rate of reaction between bromine and naphthalene is only slightly greater than the corresponding rate in acetic acid, and the order *n* (M/5—M/10) was found to be 3·6. In acetic acid containing carbon tetrachloride, the rate, as expected, is considerably reduced. Under drastic conditions in aqueous acetic acid the second-order mechanism may be established, as was observed for 1-chloronaphthalene in acetic acid containing 49% of water at 52° (*n*, M/80—M/160, 2·0).

Acids are catalysts for substitution in acetic acid. Thus for naphthalene at 25°, bromine substitution is catalysed ten-fold by M/2-perchloric acid, and the kinetic order is reduced to 3·6 (M/5—M/10). In strongly aqueous acetic acid, however, catalysis by acids is relatively slight. It would appear, therefore, that acid catalysis is due to proton transfer to one of the intermediates in the reaction, this transfer being more easily effected by $H_2OAc^{\oplus}$ than by $H_3O^{\oplus}$ (cf. acid catalysis of addition to αβ-unsaturated aldehydes, *J.*, 1945, 888). We assume that this proton transfer assists in the removal of hydrogen bromide to complete the substitution process.

The exact nature of the intermediates concerned in the reaction cannot be decided with certainty. In particular, it is not clear whether Br_4 is a participant in the third-order reaction, though the arguments of Part I in favour of the alternative process are in no way conclusive. A reasonable possibility, consistent with the experimental facts, is as follows:

$$AH + Br_2 \longrightarrow ABr + HBr \quad \text{. . . . . second order}$$

$$AH + Br_2 \rightleftarrows AHBr_2; \quad AHBr_2 + Br_2 \longrightarrow ABr + HBr + Br_2 \quad \text{. . . . third order}$$

$$Br_2 + Br_2 \rightleftarrows Br_4; \quad AH + Br_4 \longrightarrow AHBr_2 + Br_2;$$
$$AHBr_2 + Br_2 \longrightarrow ABr + HBr + Br_2 \quad \text{. . . . fourth order.}$$

The envisaged intermediates are associations of molecules formally neutral but polarised and presumably stabilised by solvation. They are not to be regarded as "transition states"; the manner in which they contribute to the observed kinetics is believed to imply that they represent true chemical entities present in the reacting system in small but finite concentrations, possibly not stationary during the course of the reaction.

(b) *The Effect of Halogen Substituents on the Rate of Substitution.*—In order to discuss with assurance the effect of substituent groups on the rate of substitution, it is desirable to examine rate differences under conditions which isolate a single simple mechanism. Chlorination in acetic acid fulfils this condition, being a bimolecular reaction, as established by Bradfield, Jones, and their co-workers (cf. *Trans. Faraday Soc.*, 1941, **37**, 726) for phenol ethers and anilides; and by the present authors even under conditions favourable to fourth-order bromine substitution (chloronaphthalene, chlorine, in acetic acid at 25°, M/5—M/40, $n = 2{\cdot}1$). In acetic acid containing 20% of water at 24°, the following rates were obtained for the chlorination of the phenyl halides, RX, the rate for benzene being interpolated from a comparison of benzene and chlorobenzene in acetic acid containing 1% of water:

X =	H.	F.	Cl.	Br.
k_2 (l. g.-mol.$^{-1}$ min.$^{-1}$)	0·010	0·012	0·0011	0·00079
Relative rates	100	120	11	7·9

Iodo-compounds cannot be included in comparisons of rates of chlorination, since iodo-dichlorides are formed. The rates of bromination of the phenyl halides in acetic acid recorded by Lauer and Oda (*Ber.*, 1936, **69**, 978) must be regarded as fictitious; these authors neglected to correct for errors due to volatility and to impurities, and their results are many times the true rates, which we find too slow to measure. The 1-halogenonaphthalenes (R′X), however, brominate at measurable rates in acetic acid, and thus permit the inclusion of the iodo-derivative. Since substitution, at least for the initial stages of the reaction, is predominantly in the 4-position (cf. Schumann, Gueffray, and Winkelmuller, *Annalen*, 1931, **487**, 270; Hirtz, *Ber.*, 1896, **29**, 1404), ambiguities arising from variation in the ortho/para ratio are avoided. Because a high reaction order was found under the conditions of the rate measurements, three series were examined, to establish that the major rate differences were independent of the reaction order. Table I, which includes the rates of chlorination, shows that the change in experimental conditions does not affect the relative rates in such a way as to obscure the relationship between the reactivities of the compounds examined, *viz.*, R′H ~ R′F ≫ R′I > R′Cl > R′Br. The reactivity per replaceable hydrogen atom (*i.e.*, corrected for the statistical factor arising from the fact that naphthalene has four equivalent positions available for substitution) is in the order R′F > R′H > R′I > R′Cl > R′Br.

TABLE I.

Relative rates of halogenation of the 1-*halogenonaphthalenes*, R′X, *in* HOAc.

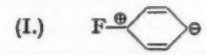
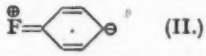
X =	H.	F.	Cl.	Br.	I.
Cl_2, M/40, 25° ($n = 2$)	100	100	6·0	5·0	—
Br_2, M/5—M/10, 25° ($n = 4$)	100	92	3·2	2·1	5·5
Br_2, M/5—M/10, 25°, $HClO_4$ M/2 ($n = 3{\cdot}5$)	100	88	2·8	1·9	3·8
Br_2, M/10—M/20, 52°, $HClO_4$ M/2 ($n = 3{\cdot}1$)	100	99	3·6	2·8	6·9

The bromination rates are more widely spaced than the chlorination rates, as was also found for the alkylbenzenes (Part II, *J.*, 1943, 279). This difference may depend on a difference in mechanism between the two reactions; whereas the rates of chlorination depend only on a velocity constant ($-\mathrm{d}[Cl_2]/\mathrm{d}t = k[A][Cl_2]$), the bromination rates depend also on an equilibrium ($-\mathrm{d}[Br_2]/\mathrm{d}t = Kk[A][Br_2]^n$, for third- or fourth-order kinetics). If K and k alter in the same sense with change in the substituent X, the bromination series will be more widely spaced than the chlorination series. The few available results in the field of halogen addition reveal a similar trend.

The influence of ring-substituted halogen on reactions and equilibria has been the subject of much discussion and controversy. Watson ("Modern Theories of Organic Chemistry", Oxford University Press, 1937, p. 76) summarises much of the evidence, which may conveniently be considered under three headings:

(i) *Physical data.* The dipole moments of the halogenobenzenes indicate an overall electron withdrawal from the aromatic nucleus, and are in the irregular order Cl ~ Br > F > I. In conjunction with the dipole moments of the alkyl halides, these values, according to Sutton (*Proc. Roy. Soc.*, 1931, **133**, *A*, 668) and Groves and Sugden (*J.*, 1937, 1992) lead to the conclusion that the halogens possess (in addition to the electron-withdrawing inductive effect, the accepted order of which is F > Cl > Br > I) a capacity for electron release to the aromatic nucleus which decreases in the order F > Cl > Br > I. Hugill, Coop, and Sutton (*Trans. Faraday Soc.*, 1938, **34**, 1518) have discussed bond-length data in relation to the above results. Extending their values by inclusion of the fluoro-compound (from the work of Finbak and Hassel, *Chem. Abstr.*, 1942,

36, 6408) we find bond shortenings (% of the normal bond-length) in the monohalogenobenzenes of 7·1% (C–F); 4·0% (C–Cl); 1·6% (C–Br); 3·8% (C–I). The contribution of the double-bonded form will follow the same irregular order, which does not agree completely with that deduced from the corresponding dipole moments. This small discrepancy being neglected, however, the relatively large shortening of the C–F bond length in fluorobenzene suggests that it is unnecessary to assume resonance forms such as (I), postulated by Bennett and his co-workers (*J.*, 1935, 1827) in order to explain the observed electron release. The experimental results are

(I.)   (II.)

on the whole consistent with the assumption that the mesomeric effect of the halogens in aromatic combination results from contribution of double-bonded structures (II). Similarly, Pauling (" The Nature of the Chemical Bond ", Cornell University Press, 1945, p. 236) deduces from interatomic distances in the polyhalogenomethanes that " chlorine has about half the power to form double bonds that fluorine has ".

(ii) *Equilibria.* The dissociation constants of the halogen-substituted acetic acids show that halogen substituents possess an inductive effect resulting in electron withdrawal in the order F > Cl > Br > I. Similar values for the *p*-halogeno-substituted phenols and phenylacetic acids confirm the conclusion from dipole-moment data that in such compounds the halogens also may release electrons mesomerically, in the order F > Cl > Br > I, which conclusion was reached independently by Bennett (*J.*, 1933, 1112), and by Bettman, Branch, and Yaabroff (*J. Amer. Chem. Soc.*, 1934, **56**, 1865). It is important to realise that the relative contribution of the inductive and mesomeric effects will differ according to the system considered. We find, therefore, as was clearly illustrated by Dippy and Lewis (*J.*, 1936, 644), that the order in which the halogen-substituted compounds fall will differ in different series. The data of Table II, taken from Watson (*op. cit.*), exemplify this point.

TABLE II.

The effects of halogen substituents on acid strengths.

Substituent (X).	H.	F.	Cl.	Br.	I.
Dissociation constant of X·CH_2·CO_2H (× 10^5)	1·8	217	155	138	75
Dissociation constant of *m*-X·C_6H_4·OH (× 10^{11})	3·2	15	49	44	39
Dissociation constant of *p*-X·C_6H_4·CH_2·CO_2H (× 10^5)	4·9	5·7	6·4	6·5	6·6
Dissociation constant of *p*-X·C_6H_4·OH (× 10^{11})	3·2	2·6	13	16	22

Dissociation constants of acids are increased by electron withdrawal. In the halogen-substituted acetic acids, as would be expected, the inductive effect controls the observed order. In the *m*-substituted phenols, a small contribution from the mesomeric effect, thought to be relayed inductively to the *m*-position, results in an irregular series. In the *p*-substituted phenylacetic acids and phenols, the mesomeric effect controls the order, and in the latter series, in which the ionizing group is conjugated with the halogen, the overall effect of fluorine as a substituent is that of electron release.

(iii) *Reaction rates.* Equilibria are determined only by the energy contents of the equilibrium states, and thus only permanent electron displacements are concerned in establishing the positions of such equilibria. The above results make it clear, however, that as far as the effects of substituent halogens on reacting systems are concerned, a wide variety of phenomena could be interpreted in terms only of the two opposing permanent displacements, which interact in such a complex fashion as to obscure the magnitude of the contribution of possible time-variable effects. As shown by the equilibria quoted in Table II, the order of electron release from halogen substituents may vary regularly in either direction, or may pass through a minimum; and the overall effect, for fluorine at least, is not necessarily that of electron withdrawal, but may be that of electron donation if the system is powerfully electron demanding. It is not surprising, therefore, that ambiguities may sometimes arise in the interpretation of reaction rates in series such as are shown in Table III. Reactions 1 and 2 (Watson, *op. cit.*) are facilitated by electron withdrawal, and exemplify the dominance of the inductive effect. Reaction 3, from the work of Bennett and Jones (*J.*, 1935, 1815), is apparently a unimolecular solvolysis facilitated by electron donation. In this series, fluorine as a substituent facilitates, and the other halogens retard the reaction. The effects here parallel those shown in the acid strengths of the *p*-halogeno-substituted phenols. Reactions 4 (Baker, *J.*, 1936, 1448; *Trans. Faraday Soc.*, 1941, **37**, 632) and 5 and 6 (Ingold and co-workers, *J.*, 1938, 918, 929) have been regarded as providing evidence for the differential contribution of a polarizability effect to the rates, and are

discussed below. Series 7 is the mean of the three bromination series given above, and (cf. series 5 and 6) is corrected for the statistical factor arising from the fact that naphthalene has four equivalent positions of attack.

TABLE III.

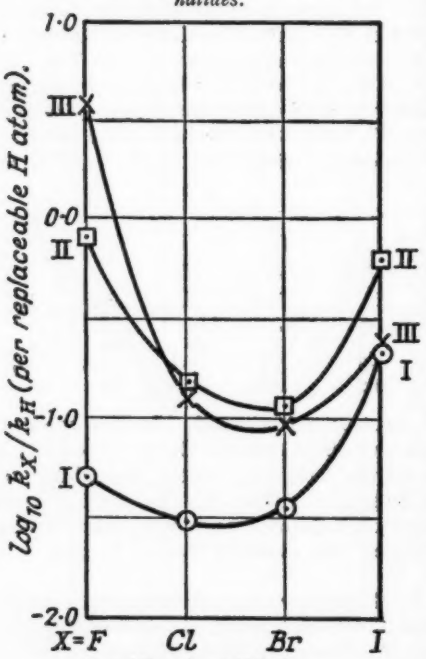
*Effects of halogen substituents on reaction rates.**

Substituent (X).	H.	F.	Cl.	Br.	I.
(1) p-X·C_6H_4·CH_2Cl + KI in acetone	1·0	1·5	3·2	2·4	2·3
(2) Alkaline hydrolysis of p-X·C_6H_4·CO_2Et	1·0	1·9	4·3	4·9	5·1
(3) p-X·C_6H_4·CH_2Cl + H_2O in 50% acetone	1·0	1·6	0·57	0·50	0·46
(4) p-X·C_6H_4·CH_2Br + C_5H_5N in acetone	1·0	1·2	1·0	1·1	1·2
(5) o-Nitration of PhX	1·0	0·05	0·030	0·034	0·2
(6) p-Nitration of PhX	1·0	0·79	0·14	0·11	0·6
(7) 4-Bromination of 1-X·$C_{10}H_7$	1·0	3·7	0·13	0·09	0·22

* Relative to the unsubstituted compound.

The relatively high velocity of bromination of fluoronaphthalene (supported by related data on fluorobenzene) provides perhaps the most convincing evidence for the operation of a polarisability factor. Dipole-moment data show that these compounds are permanently polarised in the direction of electron withdrawal from the aromatic ring; yet reactivity towards halogenation is (per replaceable hydrogen atom) increased considerably by the presence of a fluorine substituent. We have, therefore, some experimental, together with considerable theoretical reasons for assuming the existence of a polarisability factor contributing to the observed rate differences between halogen-substituted compounds. In Fig. are plotted for the electrophilic substitutions of Table III (reactions 5, 6, and 7) the values of $\log_{10}(k_{Hal.}/k_H)$, the subscripts referring to the substituent, and the rates being per replaceable hydrogen atom.

Relative rates of substitution of aromatic halides.



I, o-*Nitration of* PhX.
II, p-*Nitration of* PhX.
III, *Bromination of* 1-$C_{10}H_7X$.

The nature of the difference between curves 1 and 2 (representing o- and p-nitration respectively of the phenyl halides) may be explained as follows (cf. Lapworth and Robinson, *Mem. Proc. Manchester Lit. Phil. Soc.*, 1927, **72**, 43). Since the deactivating influence of the inductive effect is expected to decrease with distance from the controlling dipole, it must be relatively highly effective for o-substitution. The mesomeric effect, on the other hand, for reasons of symmetry (cf. *Trans. Faraday Soc.*, 1941, **37**, 745) will be relayed more powerfully to the p- than to the o-position. Accordingly, o- as compared with p-nitration is powerfully deactivated. This deactivation, as shown by the decreasing divergence of curves 1 and 2 (see fig.), is least for iodobenzene and greatest for fluorobenzene, thus decreasing with the inductive effect of the substituent, despite the probability that steric hindrance of substitution would oppose this tendency.

In comparing curves 2 (p-nitration) and 3 (4-bromination) we neglect differences shown in Table I dependent on the order of the reaction. These are small, and would not invalidate our conclusions. We are also forced to neglect possible differences between the phenyl and the naphthyl series, as ortho/para ratios are not available under the conditions of kinetic measurement, and the critical value for the iodo-compound is not accessible. The virtual identity of the dipole moments of each pair of compounds (PhF, $C_{10}H_7F$, etc.) is, however, an indication that one of the controlling factors, namely, the permanent polarisation of the molecule, is similar in the two series. With the above reservations, the observed differences can be interpreted in terms of the differences between the attacking reagents. The permanent polarisation of the aromatic compound (roughly measured by the dipole moment, Cl ~ Br > F > I) is expected to result in a more powerful repulsion of the $NO_2^{\oplus}$ ion (which is the

effective nitrating agent) than of the formally neutral bromine molecule. From the figure it is clear, however, that nitration as compared with bromination is deactivated only for the fluoro-compound. For the other three compounds, nitration is activated, very slightly for the chloro-, rather more for the bromo-, and considerably for the iodo-derivative. If the above interpretation of the deactivation of the fluoro-compound is accepted, therefore, we require an effect resulting in activation of nitration as compared with bromination, and decreasing in the order I > Br > Cl > F. This is the order postulated by Baker and by Ingold for the electromeric effect. We interpret the experimental observations as signifying that a positive ion ($NO_2^{\oplus}$), as compared with a formally neutral molecule (Br_2 or Br_4), evokes the polarisability effect more powerfully, since its disturbing electrostatic field is greater. One might venture to predict that nitration involving attack by a molecular nitrating agent (*e.g.*, the N_2O_5 molecule) would result in a rate series for nitration approximating more closely to that observed for bromination. The importance of the overall permanent deactivation of the aromatic compound, as shown by the dipole moments and by the fact that nitration is deactivated relative to the unsubstituted compound for all the halogen-substituted benzenes, accounts for the partial success of the calculations of Ri and Eyring (*J. Chem. Physics*, 1940, **8**, 433), who assumed that the relative rates of nitration at different positions in the benzene ring are determined only by the distribution of electrostatic charges on the carbon atoms at which substitution is occurring.

The theoretically expected order in which halogen substituents would provide an electromeric electron release is not agreed. Bennett *et al.* (*loc. cit.*) assumed that it would follow the order of the mesomeric effect F > Cl > Br > I, but that the operation of a polarisability factor in the order I > Br > Cl > F sufficed to account for the fact that the substitution of *o*-chlorofluorobenzene is predominently *para* to the fluorine atom, whereas *o*-bromoiodobenzene is substituted to a greater extent *para* to iodine (Ingold and Vass, *J.*, 1928, 417; Holleman,

Rec. Trav. chim., 1915, **34**, 204). Bird and Ingold, on the other hand (*J.*, 1938, 918), assumed that an electromeric polarisability in the order I > Br > Cl > F contributed to the rate differences in the nitration of the halogenobenzenes, since they regarded this reaction as highly suitable for the observation of such electron displacements. The irregular series quoted above from the work of Baker (Table III, reaction 4), was thought by the latter author to suggest the operation of an electromeric effect in the same order. In the latter case it is interesting that all the halogens appear to be electron donating, though the differences are small and the polar character of the reaction is theoretically uncertain.

Our experimental results appear to be explained most readily on the assumption that we are observing a polarisability effect, the order of which is I > Br > Cl > F. If this is accepted, and if also it is agreed that in the system under consideration we can neglect inductomeric as compared with electromeric polarisability, then it must be concluded that Bennett's order for the electromeric effect, which has recently been supported by Remick (" Electronic Interpretations of Organic Chemistry ", John Wiley and Sons, N.Y., 1943), is incorrect. An alternative possibility is that we have observed the effect of inductomeric polarisability of the C–Halogen bond. Such a disturbance, partially reversing the permanent inductive polarisation, should vary with the halogen in the manner found, and should, comparing as reagents the $NO_2^{\oplus}$ ion and the Br_2 molecule, be considerably more powerfully evoked by the electrostatic field of the positive ion. Insofar as we have considered only differences between nitration and bromination, we cannot on this basis make any deductions concerning the total polarisability effect. The latter might still be in the order F > Cl > Br > I, and particularly is this possible for halogenation, for which reaction we theoretically expect inductomeric disturbances to be relatively small, and, for which, experiment shows an unexpectedly great reactivity for the fluoro-substituted compound.

Experimental.

The technique, both for bromination and for chlorination, has been given in Parts I and II (*loc. cit.*), where are described some of the compounds used in this work, together with certain of the results used in the present discussion. Methyl alcohol was Baker's " Analysed ", and reacted inappreciably with bromine under the conditions of the kinetic measurements. The following additional compounds were examined: 1-fluoronaphthalene, E.K., redistilled, b. p. 90—91° (*ca.* 15 mm.); 1 -chloronaphthalene, E.K., redistilled, b. p. 152—153° (*ca.* 30 mm.), $n_D^{20°}$ 1·634; 1-bromonaphthalene, E.K., redistilled, b. p. 60—63° (*ca.* 0·1 mm.), $n_D^{20°}$ 1·658; 1-iodonaphthalene, E.K., redistilled, b. p. 156° (*ca.* 15 mm.); fluorobenzene, prepared from benzenediazonium borofluoride, b. p. 85° 760 mm.), $d_{15°}^{15°}$ 1·031;

chlorobenzene, B.D.H., redistilled, b. p. 132° (756 mm.); bromobenzene, B.D.H., redistilled, b. p. 155° (760 mm.); *N*-methylacetanilide, recrystallised, m. p. 103°.

Solutions of perchloric acid in acetic acid were prepared as described elsewhere (*J.*, 1945, 888). The following results are for the bromination of the 1-halogenonaphthalenes, $C_{10}H_7X$, as times (min.) for $x = 10\%$ absorption of bromine in acetic acid:

X =	H.	F.	Cl.	Br.	I.
Reactants M/5, 25°	4·6	5·5	139	222	91
Reactants M/10, 25°	37·0	37·3	1170	1800	620
Reactants M/5, M/2-$HClO_4$, 25°	0·4	0·5	14·0	22·0	10·0
Reactants M/10, M/2-$HClO_4$, 25°	2·3	2·4	81	122	63
Reactants M/10, M/2-$HClO_4$, 52°	1·0	1·0	28	36	14
Reactants M/20, M/2-$HClO_4$, 52°	4·3	4·4	120	148	64

The following are similar values for other bromine substitutions, in acetic acid at 25°, except where otherwise stated.

Naphthalene at 24°; M/5, 4·8; M/10, 38·6; M/5, Br_2 M/10, 18·5. In acetic acid containing 1% water, at 24°: M/5, 3·0; M/10, 24·1. In acetic acid containing 50% CCl_4, M/5, 55. In methyl alcohol, M/5, 3·4; M/10, 18·1.

1-Chloronaphthalene, in acetic acid containing 17% water, M/5, 3·5: M/10, 21·5 (+ 0·169M-$HClO_4$, 19); M/20, 110. In acetic acid containing 49% water, at 52°, $x = 20$, M/80, 8·1; M/160, 16·0.

1-Bromonaphthalene M/5, Br_2 M/10, 815.

For chlorinations, the following times were obtained (minutes, $x = 20\%$ reaction, reactants each M/40 in acetic acid at 25°, except where otherwise stated): naphthalene, 2·4; 1-fluoronaphthalene, 2·5; 1-chloronaphthalene, 45 (M/5, 4·6); 1-bromonaphthalene, 54. The k_2 values given for the halogenobenzenes are the mean of three or more concordant measurements, with aromatic compound M/5, Cl_2 M/20.

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26. *The Application of Pfitzinger Reactions to the Synthesis of Quinoline Derivatives: A Novel Route to 4-Hydroxyquinolines.*

By Ng. Ph. Buu-Hoï and René Royer.

In continuation of earlier work (Buu-Hoï, *J.*, 1946, 795) upon the effect of steric hindrance on the course of Pfitzinger reactions, the condensations of isatins and methyl ketones are shown to involve mostly the methyl group, except in the case of methyl ethyl ketone; pinacoline gave only traces of condensation products. Symmetrical dialkyl ketones react normally, except in the case of highly branched ketones such as di*iso*butyl ketone.

In many instances, the pyrolysis of 2-alkylcinchoninic acids is shown to afford not only the expected 2-alkylquinolines through decarboxylation, but also the corresponding 4-hydroxy-2-alkylquinolines, through decarbonylation.

In recent papers (Buu-Hoï, *loc. cit.*; Buu-Hoï and Cagniant, *Bull. Soc. chim.*, 1946, **13**, 123), Pfitzinger reactions between isatins and alicyclic or arylaliphatic ketones $Ar{\cdot}CO{\cdot}CH_2R$ have been shown to be highly sensitive towards steric hindrance. These studies have now been extended to methyl alkyl ketones and to symmetrical dialkyl ketones.

Pfitzinger (*J. pr. Chem.*, 1897, **56**, 283) found that methyl ethyl ketone reacts with isatin to give 2 : 3-dimethylcinchoninic acid; we have confirmed this work, and this proves that the methylene belonging to an ethyl group is far more reactive than the methyl group, this observation being consistent with previous experiments bearing upon the halogenation of ethylenic hydrocarbons (Ziegler, *et al.*, *Annalen*, 1942, **551**, 80) and alkylnaphthalenes (Buu-Hoï and Lecocq, *J.*, 1946, 830) by means of *N*-bromoamides. These observations may readily be accounted for on the basis of the theory of hyperconjugation (cf. Buu-Hoï and Daudel, *Rec. Trav. chim.*, 1946, **65**, 731).

Surprisingly, this effect is completely reversed in the case of higher homologues of the ethyl radical, the methylene group becoming less active than the methyl. Thus, isatin reacts with methyl *n*-propyl ketone to give, as the chief product, 2-*n*-propylcinchoninic acid, which has previously been synthesised in a different way (Tonella, *Rec. Trav. chim.*, 1897, **16**, 361), although there was some evidence of the presence of a higher-melting isomeric acid. Similarly, methyl *iso*butyl ketone and isatin give the already known 2-*iso*butylcinchoninic acid (Doebner,

Annalen, 1887, **242**, 282). The homogeneous reaction products from isatin with methyl *n*-hexyl ketone and with methyl *n*-nonyl ketone must then be considered as 2-*n*-hexyl- and 2-*n*-nonyl-cinchoninic acid. This assumption was proved by chromic acid oxidation of the corresponding alkylquinolines, *n*-valeric acid being obtained in the former case, and *n*-octoic acid in the latter.

From the results of those experiments, it may be inferred that Pfitzinger reactions performed with homologues or halogen derivatives of isatin must take the same course. In this respect, a series of cinchoninic acids bearing substituents on both benzenoid and pyridinic nuclei have been obtained by combining 5-methylisatin, 5-bromoisatin, and 5 : 7-dichloroisatin with the above-mentioned methyl alkyl ketones : details are given later. Owing to steric hindrance, only traces of reaction products could be obtained from condensation of pinacolin with isatin and 5-bromoisatin.

The Pfitzinger reaction between isatins and symmetrical dialkyl ketones occurs normally, except when a strong steric hindrance is present in the ketonic molecule. Thus, isatin and di-*n*-propyl ketone gave high yields of 3-ethyl-2-*n*-propylcinchoninic acid, whereas di*iso*butyl ketone did not give appreciable amounts of the normal condensation products either with isatin or with 5-bromoisatin. Even high-molecular ketones such as palmitone (n-$C_{15}H_{31})_2CO$ react (palmitone and isatin give the low-melting 3-n-*tetradecyl*-2-n-*pentadecylcinchoninic acid*).

Since the earlier work (*e.g.*, Koenigs, *Ber.*, 1879, **12**, 98; Doebner, *loc. cit.*), decarboxylation of cinchoninic acids by heating them either alone or in the presence of lime or soda-lime has frequently been used for the synthesis of substituted quinolines. We have now found that the simple dry distillation of substituted cinchoninic acids without any alkaline catalyst affords not only a very convenient method of preparation for homologues and halogen derivatives of quinoline, but this technique also leads in many instances to the corresponding 4-hydroxy-quinolines, the pyrolysis resulting sometimes in a loss of carbon monoxide. In those cases, the presence of carbon monoxide among the gaseous pyrolysis products was detected by means of iodic anhydride.

For example, distillation of 2-methylcinchoninic acid gave a mixture of quinaldine and 4-hydroxy-2-methylquinoline; in the same manner, 6-bromo-4-hydroxyquinaldine was obtained along with 6-bromoquinaldine from 6-bromo-2-methylcinchoninic acid prepared from acetone and 5-bromoisatin.

Similarly, small quantities of 4-hydroxy-2 : 3-dimethylquinoline could be detected in the distillation products from 2 : 3-dimethylcinchoninic acid. 2-*n*-Propylcinchoninic acid yielded 2-*n*-propylquinoline, whereas its 6-bromo-derivative gave rise almost entirely to 6-bromo-4-hydroxy-2-*n*-propylquinoline; 2-*iso*butylcinchoninic acid afforded a mixture of 2-*iso*butyl- and 4-*hydroxy*-2-iso*butyl*-quinoline. In some cases, pyrolysis proceeded as expected, as, for instance, 6-*bromo*-2-iso*butylcinchoninic acid* afforded a mixture of 6-*bromo*-2-iso*butylquinoline* with its 4-*hydroxy*-derivative, but 6 : 8-*dichloro*-2-iso*butylcinchoninic acid* yielded only 6 : 8-*dichloro*-4-*hydroxy*-2-iso*butylquinoline*. On the other hand, from the distillation products of 6-*methyl*-2-iso*butylcinchoninic acid*, only 6-*methyl*-2-iso*butylquinoline* could be isolated. Nevertheless, the promoting effect of the presence of substituents in the molecules of the related cinchoninic acids upon the formation of 4-hydroxyquinolines is shown by the following examples. Whereas 2-n-*hexyl*- and 6-*methyl*-2-n-*hexyl-cinchoninic acid* gave rise to 2-n-*hexyl*- and 6-*methyl*-2-n-*hexyl-quinoline* respectively, the distillation of 6 : 8-*dichloro*-2-n-*hexylcinchoninic acid* afforded a mixture of 6 : 8-*dichloro*-4-*hydroxy*-2-n-*hexylquinoline* and a small quantity of the non-hydroxylic compound, isolated as its *picrate*. 2-n-*Nonylcinchoninic acid* was readily decarboxylated to 2-n-*nonylquinoline*, whereas 6-*methyl*-2-n-*nonylcinchoninic acid* gave rise only to 4-*hydroxy*-6-*methyl*-2-n-*nonylquinoline*; 6-*bromo*-2-n-*nonylcinchoninic acid* afforded 6-*bromo*-4-*hydroxy*-2-n-*nonylquinoline*, along with traces of 6-bromo-2-*n*-nonylquinoline (*picrate*). An apparent exception to this rule is afforded by 6-*bromo*-2-n-*hexylcinchoninic acid*, which gave the corresponding 6-*bromo*-2-n-*hexylquinoline* as the sole isolable pyrolysis product.

This new route to 4-hydroxyquinolines may be useful for the preparation of compounds of this class not accessible through the Conrad–Limpach synthesis. Investigations along these lines are being continued.

Experimental.

Pyrolysis of 2 : 3-*Dimethylcinchoninic Acid.*—This acid was prepared (yield 10 g.) from isatin (10 g.), methyl ethyl ketone (15 g.), and potassium hydroxide (14 g.) dissolved in water (70 c.c.); m. p. > 310°. It was thoroughly dried at 100°, and heated in a vacuum; the distillate, which partly solidified on cooling, was treated with cold alcohol, and the insoluble portion recrystallised from toluene, thus giving 4-hydroxy-2 : 3-dimethylquinoline (0·2 g.) as colourless needles, m. p. 310° (Conrad and Limpach, *Ber.*, 1891, **24**, 2991, gave m. p. 305°). On treatment with picric acid, the alcoholic filtrate (above) gave

2 : 3-dimethylquinoline picrate (6 g.) in silky yellow needles, m. p. 227° (from alcohol) (Pfitzinger, *loc. cit.*, gave m. p. 229°).

6-*Bromo*-2 : 3-*dimethylcinchoninic Acid.*—A mixture of 5-bromoisatin (5 g.), methyl ethyl ketone (5·5 g.), and potassium hydroxide (6 5 g.), dissolved in water (50 c.c.), was treated as above. The cinchoninic *acid* thus obtained (6 g.) crystallised from alcohol in prismatic colourless needles, m. p. 290—291° (Found: N, 5·2. $C_{12}H_{10}O_2NBr$ requires N, 5·0%). Dry distillation of this acid (4 g.) in a vacuum (10 mm.) gave a thick yellowish jelly, which was dissolved in hot benzene and converted into a *picrate* (3 g.); this was almost insoluble in alcohol, and crystallised from toluene in fine bright yellow needles, m. p. 225° (decomp. above 200—205°) (Found: N, 11·9. $C_{11}H_{10}NBr,C_6H_3O_7N_3$ requires N, 12·0%). This picrate yielded on treatment with aqueous ammonia 6-*bromo*-2 : 3-*dimethylquinoline*, which crystallised from light petroleum in colourless silky needles, m. p. 82° (Found: N, 6·0. $C_{11}H_{10}NBr$ requires N, 6·3%).

6 : 8-*Dichloro*-2 : 3-*dimethylcinchoninic Acid.*—5 : 7-Dichloroisatin (2·5 g.), methyl ethyl ketone (3 g.), and potassium hydroxide (3·5 g.) dissolved in water (30 c.c.) gave a moderate yield of this *acid* (1 g.), which crystallised from aqueous alcohol in almost colourless prismatic needles which decomposed progressively on heating, without melting below 305° (Found: N, 5·4. $C_{12}H_9O_2NCl_2$ requires N, 5·1%).

Pyrolysis Experiments with 2-*Methylcinchoninic Acid.*—On dry distillation under atmospheric pressure this acid (14 g.) gave a mixture of quinaldine (5 g.), b. p. 245—246°, characterised by its picrate, m. p. 194° (Ciamician and Silber, *Ber.*, 1905, **38**, 3816), and of a solid product (5 g.) which crystallised from alcohol in colourless, readily sublimable leaflets, m. p. 242° (Found: N, 8·8. Calc. for $C_{10}H_9ON$: N, 8·7%), not depressed by admixture with a sample of 4-hydroxyquinaldine prepared by means of the Conrad–Limpach reaction (*Ber.*, 1887, **20**, 947). The gaseous products of the pyrolysis contained both carbon monoxide and dioxide.

6-*Bromo*-2-*methylcinchoninic Acid.*—A mixture of 5-bromoisatin (5 g.), acetone (5 g.), and potassium hydroxide (6·5 g.) dissolved in water (40 c.c.) was refluxed during 16 hours, and the dark brown solution twice extracted with ether, evaporated to half bulk, filtered from the deposited tarry material, and acidified with acetic acid. After cooling, the thick magma of needles thus obtained was filtered off and crystallised from 50% aqueous alcohol. 6-*Bromo*-2-*methylcinchoninic acid* (3 g.) formed glistening, slightly yellowish prisms, m. p. 269° (decomp. above 255°) (Found: N, 5·1. $C_{11}H_8O_2NBr$ requires N, 5·3%). The solid mass obtained on vacuum pyrolysis was triturated with a small quantity of cold ethanol, and the insoluble product (0·1 g. from 2 g. of the cinchoninic acid) crystallised from boiling alcohol; 6-*bromo*-4-*hydroxyquinaldine* formed slightly yellowish needles which readily sublimed above 230° and melted at 269° (Found: N, 5·9. $C_{10}H_8ONBr$ requires N, 5·8%). The alcoholic filtrates gave on treatment with an excess of picric acid a *picrate* (1 g.), which crystallised from toluene in glistening yellow needles, m. p. 205° (sintering above 190°) (Found: N, 12·2. $C_{19}H_8NBr,C_6H_3O_7N_3$ requires N, 12·4%). Decomposition of this picrate by means of aqueous ammonia gave 6-bromoquinaldine, which formed colourless needles, m. p. 100° from light petroleum (Bartow and MacCollum, *J. Amer. Chem. Soc.*, 1904, **26**, 704, gave m. p. 96—97°).

2-n-*Propylcinchoninic Acid.*—A mixture of isatin (15 g.), methyl *n*-propyl ketone (10 g.), and potassium hydroxide (19 g.) dissolved in 10% aqueous alcohol was refluxed during 18 hours. After standard treatment (including concentration to small bulk on a water-bath), the apparently heterogeneous solid obtained (13 g.) was twice recrystallised from water, yielding 2-*n*-propylcinchoninic acid (8 g.) in glistening, silky, colourless leaflets, m. p. 156° (Tonella, *loc. cit.*, gave m. p. 152·8°). A higher-melting isomeric acid was detected in the mother-liquors, but could not be obtained pure. The yellowish oil obtained in the pyrolysis of 2-*n*-propylcinchoninic acid afforded, on redistillation, pure 2-*n*-propylquinoline, b. p. 205°/70 mm., $n^{17\cdot1°}$ 1·5900; the corresponding picrate had m. p. 159—160° (Delaby and Hiron, *Bull. Soc. chim.*, 1930, **47**, 1398, gave b. p. 142—145°/13 mm. and m. p. 159°, respectively). No hydroxyquinoline could be detected.

6-*Bromo*-2-n-*propylcinchoninic Acid.*—5-Bromoisatin (2 g.), methyl *n*-propyl ketone (2 g.), and potassium hydroxide (3 g.) dissolved in 30% aqueous alcohol (20 c.c.) gave a cinchoninic *acid* (1·5 g.), which formed fine, glistening, yellowish needles, m. p. 212° from methanol (Found: N, 4·8. $C_{13}H_{12}O_2NBr$ requires N, 4·7%). Pyrolysis of this acid under 1 mm. yielded a solid brown product, which, after two recrystallisations from methanol, gave 6-*bromo*-4-*hydroxy*-2-n-*propylquinoline* (0·5 g.) as glistening, yellowish needles, m. p. 214° (Found: N, 5·4. $C_{12}H_{12}ONBr$ requires N, 5·2%). No picrate could be obtained in pure condition from the mother-liquors.

2-iso*Butylcinchoninic Acid.*—Methyl *iso*butyl ketone (9 g.), isatin (10 g.), and potassium hydroxide (13 g.) in 20% aqueous alcohol (40 c.c.) gave after 24 hours' heating 2-*iso*butylcinchoninic acid (8·3 g.), which crystallised from very dilute aqueous alcohol in glistening, colourless needles, m. p. 192° (Doebner, *loc. cit.*, gave m. p. 186°). Pyrolysis of this acid (7 g.) afforded a yellow oil which partly solidified, and was therefore triturated with small quantities of cold ethanol. The remaining 4-*hydroxy*-2-iso*butylquinoline* (0·8 g.) was filtered off, and recrystallised from dilute alcohol; silky, colourless needles, m. p. 189°, very soluble in alcohol, were thus obtained (Found: N, 7·1. $C_{13}H_{15}ON$ requires N, 6·9%). The alcoholic filtrate was evaporated, and the residue redistilled in a vacuum, giving 2-*iso*butylquinoline (3 g.), b. p. 268—270°, which yielded a picrate crystallising from alcoholic benzene in long, silky, golden-yellow needles, m. p. 164° (Doebner, *loc. cit.*, gave m. p. 161°).

6-*Methyl*-2-iso*butylcinchoninic Acid.*—5-Methylisatin (4·3 g.), methyl *iso*butyl ketone (5·2 g.), and potassium hydroxide (5·5 g.) dissolved in 30% aqueous alcohol (30 c.c.) gave 6-*methyl*-2-iso*butylcinchoninic acid* (3 g.), which crystallised from methanol in silky, colourless needles, m. p. 192° (Found: N, 5·6. $C_{16}H_{17}O_2N$ requires N, 5·7%). Pyrolysis of this product (2 g.) yielded a viscous oil, which was redistilled in a vacuum. 6-*Methyl*-2-iso*butylquinoline* thus obtained (1 g.) was a yellowish liquid with a pleasant aromatic smell, b. p. 180°/20 mm., $n^{16°}$ 1·5766 (Found: N, 7·0. $C_{14}H_{17}N$ requires N, 7·1%), and gave a *picrate* crystallising from alcohol–benzene in glistening yellow needles, m. p. 156° (Found: N, 13·2. $C_{14}H_{17}N,C_6H_3O_7N_3$ requires N, 13·0%). No traces of hydroxyquinoline could be obtained.

6-*Bromo*-2-iso*butylcinchoninic Acid.*—Methyl *iso*butyl ketone (7 g.), 5-bromoisatin (16 g.), and

potassium hydroxide (20 g.) in 20% aqueous alcohol (50 c.c.) gave a cinchoninic *acid* (10 g.), which formed glistening, silky, yellowish needles, m. p. 189°, from dilute ethanol (Found: N, 4·4. $C_{14}H_{14}O_2NBr$ requires N, 4·5%). Standard treatment of the pyrolysis products obtained from this acid (8·5 g.) gave 6-*bromo*-4-*hydroxy*-2-iso*butylquinoline* (2 g.) which crystallised from alcohol–benzene in colourless, alkali-soluble prisms, m. p. 191—192° (Found: N, 5·1. $C_{13}H_{14}ONBr$ requires N, 5·0%), and 6-*bromo*-2-*isobutylquinoline* (3 g.) as a pleasant smelling, viscous, yellowish oil, b. p. 215°/14 mm., which slowly solidified; after recrystallisation from light petroleum, colourless prisms, m. p. 46°, were obtained (Found: N, 5·3. $C_{13}H_{14}NBr$ requires N, 5·3%). The corresponding *picrate* formed a microcrystalline, yellow powder, m. p. 192°, from benzene (Found: N, 11·2. $C_{13}H_{14}NBr,C_6H_3O_7N_3$ requires N, 11·5%).

6 : 8-*Dichloro*-2-iso*butylcinchoninic Acid*.—5 : 7-Dichloroisatin (3·4 g.), methyl *iso*butyl ketone (3 g.), and potassium hydroxide (5 g.) dissolved in 40% aqueous alcohol (25 c.c.) gave the *acid* (3 g.), which crystallised from alcohol in fine, glistening, yellowish needles, m. p. 186° (Found: N, 4·6. $C_{14}H_{13}O_2NCl_2$ requires N, 4·7%). Pyrolysis of this acid (2 g.) in a high vacuum (1 mm.) yielded 6 : 8-*dichloro*-4-*hydroxy*-2-iso*butylquinoline* (1 g.), which formed colourless, glistening prisms, m. p. 186°, from methanol (Found: N, 5·0. $C_{13}H_{13}ONCl_2$ requires N, 5·2%).

2-n-*Hexylcinchoninic Acid*.—Octan-2-one (10 g.), isatin (10 g.), and potassium hydroxide (12 g., dissolved in 10 c.c. of water and 15 c.c. of alcohol) gave a homogeneous *acid* (15 g.), which formed tiny, colourless prisms, m. p. 139—140°, from methanol (Found: N, 5·2. $C_{16}H_{19}O_2N$ requires N, 5·4%). The alkaline solutions of this acid gave a persistent foam when shaken. Pyrolysis of the acid (10 g.) yielded 2-n-*hexylquinoline* (5 g.) as a yellow, mobile oil with a pleasant smell; b. p. 298—300°, $n^{18\cdot5°}$ 1·5620 (Found: N, 6·4. $C_{15}H_{19}N$ requires N, 6·5%), which gave a *picrate*, crystallising from ethanol in long, yellow needles, m. p. 112° (Found: N, 12·4. $C_{15}H_{19}N,C_6H_3O_7N_3$ requires N, 12·6%). A mixture of the foregoing quinoline (4 g.) with chromic acid (4 g.) dissolved in dilute sulphuric acid (40 c.c. of water; 5 g. of acid) was boiled during one hour, and the reaction product steam-distilled. *n*-Valeric acid was thus obtained and characterised by the m. p. of its diamide with 1 : 5-diaminonaphthalene (cf. Buu-Hoï, *Bull. Soc. chim.*, 1945, **12**, 590).

6-*Bromo*-2-n-*hexylcinchoninic Acid*.—5-Bromoisatin (3 g.), octan-2-one (1·7 g.), and potassium hydroxide (3·3 g.) dissolved in 50% aqueous alcohol (30 c.c.) yielded, after 18 hours' heating, the expected cinchoninic *acid* (3·5 g.). This crystallised from ethanol in slightly yellowish, silky needles, m. p. 152—153° (Found: N, 4·2. $C_{16}H_{18}O_2NBr$ requires N, 4·1%). Vacuum pyrolysis of this acid (2·8 g.) afforded, after redistillation, 6-*bromo*-2-n-*hexylquinoline* (2 g.) as a viscous, yellow oil, b. p. 238—240°/25 mm., $n^{18\cdot1°}$ 1·5910 (Found: N, 4·8. $C_{15}H_{18}NBr$ requires N, 4·7%). The corresponding *picrate* formed fine, yellow, glistening prisms, m. p. 154°, from alcohol–benzene (Found: N, 11·0. $C_{15}H_{18}NBr,C_6H_3O_7N_3$ requires N, 10·8%).

6 : 8-*Dichloro*-2-n-*hexylcinchoninic Acid*.—5 : 7-Dichloroisatin (2 g.), octan-2-one (1·2 g.), and potassium hydroxide (2·3 g.) dissolved in 50% aqueous alcohol (20 c.c.) gave the corresponding cinchoninic *acid* (2·3 g.) as almost colourless, silky needles, m. p. 145° (from alcohol) (Found: N, 4·2. $C_{16}H_{17}O_2NCl_2$ requires N, 4·3%). Vacuum pyrolysis of this acid (2·5 g.) yielded after standard treatment 6 : 8-*dichloro*-4-*hydroxy*-2-n-*hexylquinoline* (1 g.), which crystallised from aqueous methanol in tiny, glistening, colourless prisms, m. p. 128°, extremely soluble in hot ethanol (Found: N, 4·6. $C_{15}H_{17}NCl_2$ requires N, 4·7%). The alcoholic mother-liquors afforded on treatment with picric acid a small quantity of the *picrate* of 6 : 8-dichloro-2-*n*-hexylquinoline, which formed yellow prisms, m. p. 141°, from ethanol (Found: N, 11·1. $C_{15}H_{17}NCl_2,C_6H_3O_7N_3$ requires N, 10·8%).

6-*Methyl*-2-n-*hexylcinchoninic Acid*.—This *acid* (2 g.) was obtained from 5-methylisatin (2 g.) and octan-2-one (1·6 g.), and formed slightly yellowish, silky needles, m. p. 159°, from ethanol (Found: N, 5·2. $C_{17}H_{21}O_2N$ requires N, 5·1%). Its pyrolysis afforded as the sole isolable product 6-*methyl*-2-n-*hexylquinoline* as a yellowish oil, b. p. 218—220°/60 mm. (Found: N, 6·3. $C_{16}H_{21}N$ requires N, 6·1%), which gave a *picrate* crystallising from ethanol in glistening, yellow prisms, m. p. 114° (Found: N, 12·5. $C_{16}H_{21}N,C_6H_3O_7N_3$ requires N, 12·3%).

2-n-*Nonylcinchoninic Acid*.—Isatin (7 g.), undecan-2-one (15 g.), and potassium hydroxide (9 g.) gave excellent yields of 2-n-*nonylcinchoninic acid* (15 g.), which formed silky, soft, colourless needles, m. p. 145°, from ethanol (Found: N, 4·8. $C_{19}H_{25}O_2N$ requires N, 4·7%). The alkaline solutions of this acid gave a strong persistent foam when shaken in a test-tube. On pyrolysis, 2-n-*nonylquinoline* (12 g.) was obtained in the form of a yellowish oil, b. p. 230—232°/25 mm.; $n^{16\cdot5°}$ 1·5470 (Found: N, 5·4. $C_{16}H_{15}N$ requires N, 5·5%), which gave *n*-octoic acid by treatment with chromic acid, following the same procedure as for the hexyl derivative. The correspodning *picrate* crystallised from ethanol in bright yellow, glinting prisms, m. p. 96° (Found: N, 11·8. $C_{19}H_{25}N,C_6H_3O_7N_3$ requires N, 11·5%).

6-*Methyl*-2-n-*nonylcinchoninic Acid*.—Condensation of 5-methylisatin (0·5 g.) with undecan-2-one (0·8 g.) in the presence of potassium hydroxide (0·7 g.) dissolved in 50% aqueous alcohol (15 c.c.) resulted in the formation of a cinchoninic acid (1·1 g.), which crystallised from hot alcohol in almost colourless, silky needles, m. p. 152—153° (Found: N, 4·6. $C_{20}H_{27}O_2N$ requires N, 4·4%). Vacuum pyrolysis of this acid gave 4-*hydroxy*-6-*methyl*-2-n-*nonylquinoline* (0·5 g.) as a microcrystalline, yellowish powder, m. p. 154° (Found: N, 5·0. $C_{19}H_{27}ON$ requires N, 4·9%). No traces of picrate of a non-hydroxylated quinoline could be isolated.

6-*Bromo*-2-n-*nonylcinchoninic Acid*.—This *acid* (2·7 g.) was obtained from 5-bromoisatin (2 g.) and undecan-2-one (1·5 g.), and formed silky, cream-coloured needles, m. p. 150°, from ethanol (Found: N, 3·8. $C_{19}H_{24}O_2NBr$ requires N, 3·7%). Pyrolysis of this product (2 g.) yielded after standard treatment, 6-*bromo*-4-*hydroxy*-2-n-*nonylquinoline* (0·4 g.), which crystallised from ethanol in cream-coloured prisms, m. p. 146°, the alkaline solutions of which gave a persistent foam on agitation (Found: N, 4·1. $C_{18}H_{24}ONBr$ requires N, 4·0%). As a by-product, 6-*bromo*-2-n-*nonylquinoline picrate* (0·2 g.) was obtained; it crystallised from hot ethanol in bright yellow prisms, m. p. 137° (Found: N, 9·8. $C_{18}H_{24}NBr,C_6H_3O_7N_3$ requires N, 10·0%).

3-*Ethyl*-2-n-*propylcinchoninic Acid*.—Di-*n*-propyl ketone (5·5 g.), treated with isatin (7·2 g.) and potassium hydroxide (8·5 g.) dissolved in 50% aqueous alcohol (30 c.c.), gave the corresponding

cinchoninic *acid* in excellent yield (11 g.). After crystallisation from 50% aqueous ethanol, almost colourless prisms, m. p. 214°, were obtained (Found: N, 5·6. $C_{15}H_{17}O_2N$ requires N, 5·7%).

No cinchoninic acid could be obtained from isatin and di*iso*butyl ketone, even after 6 days' heating

3-n-*Tetradecyl*-2-n-*pentadecylcinchoninic Acid*.—A mixture of palmitone (6 g.) (obtained by pyrolysis of calcium palmitate), isatin (1 g.), and potassium hydroxide (2 g.) dissolved in alcohol (30 c.c.) was refluxed during 3 days on a water-bath. Most of the solvent was removed by evaporation, and the residue twice extracted with hot water, after removal of palmitone by means of benzene, the aqueous solution was acidified with acetic acid. The yellowish precipitate of the *acid* was collected, and recrystallised several times from alcohol, soft, colourless needles (0·5 g.), m. p. 101°, extremely soluble in benzene, being thus obtained (Found: N, 2·3. $C_{39}H_{65}O_2N$ requires N, 2·4%).

The authors gratefully acknowledge their indebtedness to Dr. Ch. Mentzer for the gift of samples of some ketones mentioned in this work.

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27. *The Preparation of Some* N-*Substituted Derivatives of* p-*Toluenesulphonamide.*

By ALEXANDER D. KEMP and HENRY STEPHEN.

Derivatives of type p-$CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH{\cdot}COR$ (R = aliphatic, aromatic, or mixed aliphatic aromatic) have been prepared.

Aroylation was achieved by three methods. Some new substituted benzamidines have been prepared from p-toluenesulphon-α-chlorobenzylideneamide, p-$CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}N{:}CCl{\cdot}C_6H_5$, and the stability of the chlorine atom towards various reducing agents investigated.

THE following series of reactions was attempted in the hope of obtaining a general method for the preparation of aldehydes:

$$p\text{-}CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2 \xrightarrow{R{\cdot}CO{\cdot}Cl} p\text{-}CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH{\cdot}COR \xrightarrow{PCl_5} p\text{-}CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}N{:}CClR \xrightarrow{H_2}$$
$$p\text{-}CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}N{:}CHR \xrightarrow{H_2O} p\text{-}CH_3{\cdot}C_6H_4{\cdot}SO_2{\cdot}NH_2 + R{\cdot}CHO$$

Using similar schemes both Sonn and Muller (*Ber.*, 1919, **52**, 1927) and Staudinger (*ibid.*, 1908, **41**, 2217) prepared benzaldehyde from benzanilide. In the present case (R = C_6H_5) the reduction of the iminochloride, p-toluenesulphon-α-chlorobenzylideneamide, has not so far been effected.

Benzanilide iminochloride is reduced quite readily by stannous chloride (Sonn and Muller, *loc. cit.*) to the corresponding azomethine, $C_6H_5{\cdot}CH{:}N{\cdot}C_6H_5$. One of us (Stephen, *J.*, 1925, 1874) in an aldehyde synthesis from cyanides has reduced similar iminochlorides by means of stannous chloride and hydrogen chloride. Neither this last method nor other reducing agents—*e.g.*, sodium in alcohol, tin and hydrochloric acid, zinc dust in alcohol, zinc dust in glacial acetic acid—had any effect, except that some hydrolysis always took place. Thus the introduction of the SO_2 group into the benzanilide iminochloride type of molecule seems to reduce the mobility of the halogen considerably.

Meanwhile, other *N*-aroyl and *N*-acyl derivatives of p-toluenesulphonamide have been prepared. Three methods of aroylation were used:

(i) Dry fusion of p-toluenesulphonamide and the acid chloride at temperatures under 150°, following the method of Gerhardt and Chiozza (*Annalen*, 1853, **87**, 299; Wallach, *ibid.*, 1882, **214**, 209; Wallach and Grossman, *Ber.*, 1878, **11**, 753).

The above authors mention the decomposition of *N*-acyl sulphonamides to cyanides and sulphonic acids at temperatures above 150°. We confirmed this for the reaction between α-naphthoyl chloride and p-toluenesulphonamide. At 180° α-naphthyl cyanide and p-toluenesulphonic acid were the only products obtained. No p-toluenesulphon-α-naphthamide was detected.

(ii) In pyridine solution (Northey *et al.*, *J. Amer. Chem. Soc.*, 1939, **61**, 2950; and many recent patents, *e.g.*, B.PP. 581,932; 581,934).

(iii) By a modification of the Schotten–Baumann method of benzoylation.

When p-toluenesulphonamide was benzoylated using the ordinary procedure, poor yields were obtained together with p-toluenesulphonamide. *N*-Acyl and *N*-aroyl derivatives of p-toluenesulphonamide are strong acids (Wolkowa, *Z. Chem.*, 1870, **6**, 577; Chaplin and

Hunter, *J.*, 1937, 1118; Oxley *et al.*, *J.*, 1946, 768). At the start of the reaction, the *p*-toluenesulphonamide was present as the sodium salt, which then reacts with the acid chloride to form the *N*-acyl or *N*-aroyl derivative. Since this is more acidic than the starting material its sodium salt is produced, and the liberated *p*-toluenesulphonamide is precipitated. If two moles of sodium hydroxide are used, both sodium hydroxide and the sodium salt of *p*-toluenesulphonamide are competing for the benzoyl chloride. We therefore used the sodium salt of *p*-toluenesulphonamide (2 moles) and acid chloride (1 mole), and obtained much improved yields (calculated on acid chloride).

N-Acyl derivatives of *p*-toluenesulphonamide were prepared from the acid anhydrides. Methods as given for the preparation of *N*-acetyl-*p*-toluenesulphonamide (D.R.-P. 466,519; Chaplin and Hunter, *loc. cit.*) were modified. The reaction was strongly exothermic, and long heating was not necessary; also only a few drops of sulphuric acid were required to catalyse the reaction.

A series of substituted benzamidines of type $p\text{-}CH_3\cdot C_6H_4\cdot SO_2\cdot N{:}C(NHR)\cdot C_6H_5$ was prepared (Gerhardt, *Annalen*, 1858, **108**, 214; Wallach, *loc. cit.*; Geigy, B.P. 538,822). One of these ($R = C_6H_5$) was also prepared by the condensation of benzanilide iminochloride and *p*-toluenesulphonamide.

Experimental.

The Direct Heating Method.—Pure *p*-toluenesulphonamide (1 mole) and the corresponding acid chloride (1 mole or slightly more) were heated at 130—140° until evolution of hydrogen chloride had ceased. The crude product was then extracted with successive quantities of boiling water, dried, and crystallised from alcohol. Results are given below. In one run, using α-naphthoyl chloride, the temperature was maintained at 180°; α-naphthyl cyanide was isolated by steam distillation, m. p. 37—38° undepressed by admixture with an authentic specimen. *p*-Toluenesulphonic acid was identified by the production of *p*-cresol on potassium hydroxide fusion of the residue obtained after steam distillation.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid chloride (g.).	Yield (%).	M. p.
1. *N*-Benzoyl-	50	45	86	147°
2. N-o-*Toluoyl-*	11·5	11·5	*ca.* 5	112·5—113
3. N-m-*Toluoyl-*	5·1	5·1	2—4	132
4. N-3 : 4 : 5-*Trimethoxybenzoyl-*	16·1	21·75	54	168—169
5. N-*Phenoxyacetyl-*	20	20	49	139
6. N-β-*Naphthoyl-*	20	20	79	162·5—163
7. N-*Veratroyl-*	4·67 *	4·84	2—4	130—134 (decomp.)

* Sodium salt used.

Notes 1. Wolkowa (*loc. cit.*) gives m. p. 147—150° (Found: C, 61·1; H, 4·8. Calc. for $C_{14}H_{13}O_3NS$: C, 61·05; H, 4·8%).
2. (Found: C, 61·9; H, 5·2. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·2%.)
3. Mixed m. p. with *p*-toluenesulphonamide, 116—134° (Found: C, 62·1; H, 5·3. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·3%).
4. Mixed m. p. with 3 : 4 : 5-trimethoxybenzoic acid (m. p. 167—169°) 140—160° (Found: C, 55·8; H, 5·35. $C_{17}H_{19}O_6NS$ requires C, 55·9; H, 5·2%).
5. (Found: C, 58·9; H, 5·0. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9%.)
6. (Found: C, 66·1; H, 4·8. $C_{15}H_{15}O_3NS$ requires C, 66·5; H, 4·6%.)
7. (Found: C, 54·5; H, 5·5. $C_{16}H_{17}O_5NS,H_2O$ requires C, 54·4; H, 5·4%.) In another experiment 2·0044 g. of *N*-veratroyl-*p*-toluenesulphonamide on drying for 3 hours at 140°/60 mm. lost 0·1129 g., *i.e.*, 1·1 moles of water per mole of derivative.

Aroylation in Pyridine.—A mixture of *p*-toluenesulphonamide (1 mole) dissolved in pyridine (2 moles) and the acid chloride (1 mole) was heated on the water-bath for 75 minutes, then poured into dilute hydrochloric acid. On cooling and stirring, the oil solidified, and the solid was extracted once or twice with boiling water, dried, and crystallised from alcohol. Results are given below.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid chloride (g.).	Yield (%).	M. p.
1. *N*-Benzoyl-	5	4·12	80	147°
2. N-p-*Toluoyl-*	5·7	5·1	78	138—139
3. N-*Phenylacetyl-*	5·13	4·64	0	—
4. *N*-Veratroyl-	5·13	6·02	3—5	132—134 (decomp.)
5. *N*-3 : 4 : 5-Trimethoxybenzoyl-	3·42	4·61	2—5	152—159

Notes 2. (Found: C, 61·6; H, 5·25. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·2%.)
5. A small amount of intractable material was obtained.

Modified Schotten–Baumann Method.—*p*-Toluenesulphonamide (2 moles) was dissolved in aqueous sodium hydroxide (2 moles of 5%), and the acid chloride (1 mole) was added in small quantities at a time,

with shaking and cooling. When from 1/4 to 1/2 had been added, a precipitate of *p*-toluenesulphonamide began to form, increasing in amount as more acid chloride was added. When the addition was complete, the reaction mixture was left for 5 minutes, *p*-toluenesulphonamide collected, and the filtrate carefully acidified with concentrated hydrochloric acid. The precipitated derivative was digested several times with boiling water, then crystallised from alcohol or acetic acid. Results are given below.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid chloride (g.).	*p*-Toluene-sulphonamide recovered (g.).	Yield (%).	M. p.
1. *N*-Benzoyl-	17	7	8·3	76	147°
2. *N*-*o*-Toluoyl-	11·4	5·1	11·3	0	—
3. *N*-*m*-Toluoyl-	10·5	4·5	4·55	48	132—132·5
4. *N*-*p*-Toluoyl-	10·5	4·5	8·9	7	138—139
5. *N*-Phenylacetyl-.....	6·84	3·09	3·4	65	147·5—148·5

Note 5. (Found : C, 62·1; H, 5·3. $C_{15}H_{15}O_3NS$ requires C, 62·2; H, 5·2%.)

Formation of p-*Toluenesulphonyl*-N-*acylamides.*—*p*-Toluenesulphonamide (1 mole) was mixed with the acid anhydride (1 mole) and a few drops of concentrated sulphuric acid were added. The temperature rose rapidly, the reaction mixture becoming liquid (mixture was warmed gently, if necessary, to give a clear solution). When cold, the solid product was boiled with a little water, and the residue collected and dried. In two cases the compounds crystallised from hot water. Results are given below.

p-Toluenesulphonamide.	*p*-Toluene-sulphonamide (g.).	Acid anhydride (g.).	Yield (%).	M. p.
1. *N*-Acetyl-	5·13	3·06	90	137°
2. N-*Propionyl*-	5·13	3·9	85·6	111—112
3. N-*Butyryl*-	5·13	4·74	82	82—83

Notes 1. D.R.-P. 466,519 gives m. p. 139°; Chaplin and Hunter (*loc. cit.*) give m. p. 136—137°. We obtained the compound in needles from alcohol, mixed m. p. with *p*-toluenesulphonamide 103—116° (Found : C, 51·0; H, 5·2. Calc. for $C_9H_{11}O_3NS$: C, 50·7; H, 5·2%).

2. Needles from hot water (Found : C, 52·95; H, 5·8. $C_{10}H_{13}O_3NS$ requires C, 52·8; H, 5·8%).

3. Feathery needles from hot water (Found : C, 54·8; H, 6·3. $C_{11}H_{15}O_3NS$ requires C, 54·7; H, 6·3%).

p-*Toluenesulphon*-α-*chlorobenzylideneamide.*—This was prepared according to Wolkowa (*Ber.*, 1872, **5**, 140); m. p. 103° (Wolkowa gives m. p. 100°). Washings and crude product both smelled strongly of phenyl cyanide. Yield, 51% (Found : N, 4·7. Calc. for $C_{14}H_{12}O_2NClS$: N, 4·8%).

Substituted Benzamidines.—(*a*) *N*-*p*-Toluenesulphonylbenzamidine was prepared as follows. Dry ammonia gas was passed into a solution of *p*-toluenesulphon-α-chlorobenzylideneamide (0·5 g.), in dry ether (75 ml.), until saturated. The precipitate of ammonium chloride was removed, and from the filtrate a white solid (m. p. 146—147°) was obtained by evaporation; mixed m. p. with *N*-*p*-toluenesulphonylbenzamide 114—135°. Wolkowa (*Ber.*, 1872, **5**, 141) gives m. p. of *N*-*p*-toluenesulphonylbenzamidine as 114° (Found : N, 10·3. Calc. for $C_{14}H_{14}O_2N_2S$: N, 10·2%).

(*b*) The following method was used for the preparation of the other substituted benzamidines. *p*-Toluenesulphon-α-chlorobenzylideneamide (1·5 g.) was dissolved in dry ether (50 ml.), and the amine, in slight excess over the calculated quantity, added in solution in dry ether (25 ml.). The precipitate was left overnight, collected, washed with distilled water, and crystallised from alcohol. The following compounds were prepared by this method :

N′-p-*Toluenesulphonyl*-N-*phenylbenzamidine*, m. p. 146—147°. Yield, 86%. Also crystallises in a form, m. p. 151—152°. Mixed m. p. with *p*-toluenesulphonylbenzamide 115—145° (Found : N, 8·1. $C_{20}H_{18}O_2N_2S$ requires N, 8·0%).

The compound was also prepared from benzanilide iminochloride (10·9 g.) and *p*-toluenesulphonamide (8·7 g.) by heating for 1 hour at 100° and then for a further ½ hour at 140°. On cooling, the product solidified, and was obtained in crystals from alcohol, m. p. 127—138°. Further purification gave a product, m. p. 144—145°, undepressed by admixture with pure material prepared by the first method. Yield, 8 g. (crude).

N′-p-*Toluenesulphonyl*-N-o-*tolylbenzamidine*, m. p. 137—138°. Yield, 77%. Mixed m. p. with *p*-toluenesulphonamide 109—120° (Found : N, 7·9. $C_{21}H_{20}O_2N_2S$ requires N, 7·7%).

N′-p-*Toluenesulphonyl*-N-m-*tolylbenzamidine*, m. p. 156—157°. Yield, 84% (Found : N, 7·9%).

N′-p-*Toluenesulphonyl*-N-p-*tolylbenzamidine*, m. p. 167—168°. Yield, 89% (Found : N, 7·9%).

We wish to thank Mr. J. L. C. Marais for determinations of some of the nitrogen values. One of us (A. D. K.) thanks the South African National Research Council and Board for a grant.

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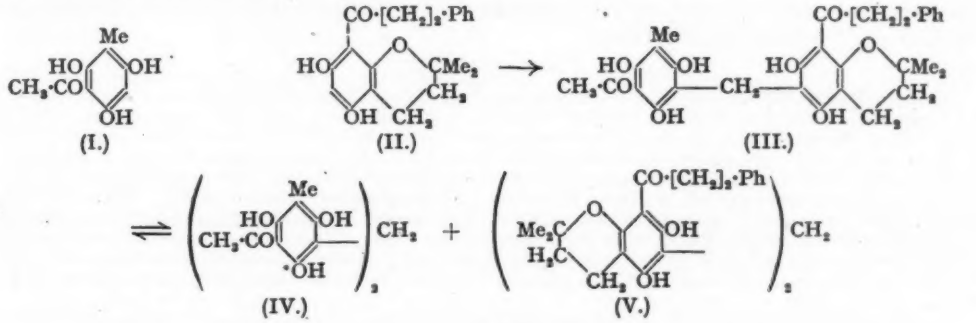
28. *Rottlerin. Part VII. The Synthesis of Tetrahydrorottlerin and of Tetrahydroallorottlerin and the Reversibility of the Rottlerone Change.*

By Thomas Backhouse, Alexander McGookin, James Matchet, Alexander Robertson, and Eric Tittensor.

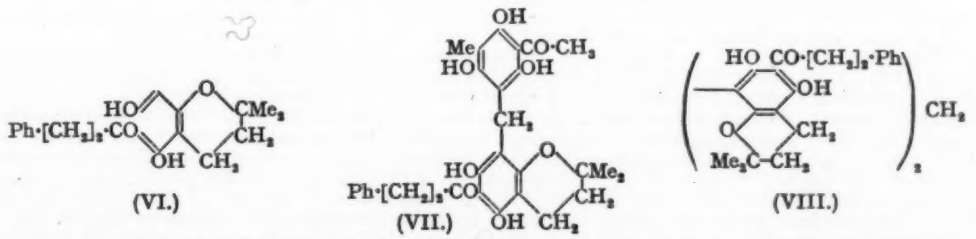
Interaction of a mixture of (I), (II), and formaldehyde in alcoholic sulphuric acid gave rise to tetrahydrorottlerin (III) in addition to (IV) and (V). Similarly tetrahydro*allo*rottlerin was obtained along with (IV) and (VIII) when the keto-chroman (II) was replaced by the isomeride (VI).

The conversion of tetrahydrorottlerin (III) into (IV) and (V) and of tetrahydro*allo*rottlerin (VII) into (IV) and (VIII) have been shown to be reversible reactions.

In Parts IV (*J.*, 1939, 1579) and V (*ibid.*, p. 1587) it was shown that the condensation of a molecule of formaldehyde with two molecules of 5 : 7-dihydroxy-8-β-phenylpropionyl-2 : 2-dimethylchroman (II) in alcoholic sulphuric acid gave rise to octahydrorottlerone (V), and similarly that *C*-methylphloracetophenone yielded the hexahydroxydiphenylmethane (IV); it therefore seemed reasonably certain that the interaction of formaldehyde with a mixture of (I) and (II) would furnish synthetic tetrahydrorottlerin (III) in addition to (IV) and (V). This objective has now been achieved and the synthetical tetrahydro-derivative (III) thus formed is identical in every way with a specimen obtained by the hydrogenation of rottlerin. In a similar manner when the keto-chroman (II) is replaced by the isomeride, 5 : 7-dihydroxy-6-β-phenylpropionyl-2 : 2-dimethylchroman (VI), tetrahydro*allo*rottlerin (VII) is formed along with (IV) and octahydro*allo*rottlerone (VIII).



(I.) (II.) (III.) (IV.) (V.)



(VI.) (VII.) (VIII.)

In Part I (*J.*, 1937, 748) it was shown that in the presence of dilute alkalis tetrahydrorottlerin like rottlerin undergoes the rottlerone change, thus showing that this reaction is entirely independent of the presence of the double bonds in the rottlerin molecule. Under these conditions, the greater part of the product consists of intractable material, presumably formed by side reactions arising on account of the reactivity of the phloroglucinol nucleus in alkaline media, and a detailed investigation of the reaction was impossible. The nature of the rottlerone change, however, was further clarified when it was subsequently discovered that the reaction can be effected in the case of tetrahydrorottlerin by means of boiling acetic acid with the formation of only small amounts of amorphous material, and that the resulting octahydrorottlerone (V) is accompanied by the hexahydroxydiphenylmethane (IV), thus accounting for the " second half " of the rottlerin molecule (Part IV, *loc. cit.*). Further, in the course of numerous experiments on the conversion of tetrahydrorottlerin into (IV) and (V) by the acetic acid method it has been observed that a proportion of the initial material was invariably recovered unchanged and hence it seemed probable that the change was a reversible

one, *i.e.*, $2(R{\cdot}CH_2{\cdot}R') \rightleftharpoons CH_2R_2 + CH_2R_2'$. This view has been conclusively established since it has been found that on being heated with acetic acid a mixture of synthetic (or natural) specimens of (IV) and (V) is partly converted into tetrahydrorottlerin (III). Similarly the conversion of tetrahydro*allo*rottlerin (VII) into octahydro*allo*rottlerone (VIII) and (IV) is also a reversible reaction because when a mixture of synthetic specimens of (IV) and (VIII) is heated in acetic acid tetrahydro*allo*rottlerin (VII) is regenerated. It may be noted that in general it has been found (unpublished results) that polyhydroxydiphenylmethane compounds undergo the same disproportionation.

These results serve to confirm the final conclusions regarding the structures of rottlerin (Part IV, *loc. cit.*), *allo*rottlerin (Part V, *loc. cit.*), and their respective derivatives, thus, *inter alia*, affording conclusive evidence of the complex nature of the reaction involved in the formation of *isoallo*rottlerin * (previously named *iso*rottlerin). Further it may be noted here that the original formula for rottlerin, first proposed by workers in this laboratory (Part II, *J.*, 1938, 309), contained all the essential features but is now known to have the orientation of *allo*rottlerin. Subsequently Brockmann and Maier (*Annalen*, 1938, **535**, 149; 1939, **541**, 53) employed this original structure for rottlerin, and as far as we are aware these authors have not modified their formulæ for the degradation and transformation products to conform with the final orientations established in Parts IV and V (*locc. cit.*). Moreover, these authors failed to interpret the complex nature of the changes obtaining in the conversion of rottlerin into *isoallo*rottlerin (cf. Mayer, "Natural Organic Colouring Matters", translated by Cook, 1943, p. 204). The compound named ψ-rottlerin by Brockmann and Maier is clearly *allo*rottlerin (formula III, Part V, *loc. cit.*), and dihydro-ψ-rottlerin is dihydro*isoallo*rottlerin, having formula type VII (Part V), both of which on hydrogenation under appropriate conditions have been found to yield tetrahydro*allo*rottlerin, m. p. 241° (not 225—226° as given by the German authors). Similarly tetrahydro-ψ-rottlerone is tetrahydro*allo*rottlerone.

Experimental.

C-Methylphloroglucinol required for the preparation of *C*-methylphloracetophenone was prepared by an improved modified method (cf. Weidel, *Monatsh.*, 1898, **19**, 224; Hein and Wagner, *Ber.*, 1935, **68**, 856). 2 : 4 : 6-Trinitrotoluene (5 g.) dissolved in absolute alcohol (250 c.c.) was reduced with hydrogen at 40 lb./sq. in. and a palladium–charcoal catalyst (from 0·2 g. of palladium chloride and 2 g. of charcoal) in the course of 3 hours, and the triamine converted into the phenol by the following procedure in which all the operations were carried out in an atmosphere of oxygen-free carbon dioxide. After addition of concentrated hydrochloric acid (8 c.c.) the catalyst was removed by filtration, the solution evaporated in a vacuum, and the residue dissolved in oxygen-free water (250 c.c.) and concentrated hydrochloric acid (4 c.c.), the mixture refluxed for 30 hours, and the resulting *C*-methylphloroglucinol isolated with ether. Purified by being twice sublimed in a high vacuum and then crystallised from benzene the phenol (1·3 g.) had m. p. 213—216°.

Treatment of a solution of 2 : 4 : 6-triaminotoluene in dilute hydrochloric acid with excess of acetic anhydride in an atmosphere of carbon dioxide gave the *triacetyl* derivative which separated from water in elongated rectangular prisms, m. p. 280° (Found : N, 15·7. $C_{13}H_{17}O_3N$ requires N, 16·0%).

Tetrahydrorottlerin.—To a solution of 5 : 7-dihydroxy-8-β-phenylpropionyl-2 : 2-dimethylchroman (Part III, *J.*, 1939, 1257) (0·41 g.) and *C*-methylphloracetophenone (Curd and Robertson, *J.*, 1933, 443) (0·25 g.) in alcohol (20 c.c.) maintained at room temperature, 40% aqueous formaldehyde (5 c.c.) was added followed by concentrated sulphuric acid (2 c.c., dropwise), and after a short time a microcrystalline yellow precipitate began to separate. Next day the product (0·56 g.) was collected, washed with water, dried, and extracted several times with cold acetone (total vol., 50 c.c.) leaving an insoluble residue which consisted of impure 2 : 4 : 6 : 2′ : 4′ : 6′-hexahydroxy-5 : 5′-diacetyl-3 : 3′-dimethyldiphenylmethane, m. p. about 265° (Part IV, *loc. cit.*). The solid left on evaporation of the acetone extracts was digested with boiling alcohol (20 c.c. in several portions), the insoluble material consisting of slightly impure octahydrorottlerone (0·1 g.), m. p. 168°, was collected, the alcoholic solution was evaporated to half its volume, and the product (0·04 g.), m. p. about 160°, which separated from the cooled residual liquor was removed. On further concentration the latter liquor then deposited tetrahydrorottlerin (0·12 g.), m. p. 211°, which on purification from alcohol formed pale yellow, elongated prisms, m. p. and mixed m. p., 214°, identical in every way with a natural specimen (Found : C, 69·3; H, 6·2. Calc. for $C_{30}H_{32}O_8$: C, 69·2; H, 6·2%). Acetylation of the synthetic product (0·05 g.) with acetic anhydride (0·3 c.c.) and pyridine (1 c.c.) at room temperature for 3 days gave the penta-acetate which formed colourless prisms, m. p. 188°, from methyl alcohol, identical with authentic *O*-penta-acetyltetrahydrorottlerin (Part I, *J.*, 1937, 753). When a solution of synthetic tetrahydrorottlerin (0·03 g.) in 4% aqueous sodium hydroxide (0·4 c.c.) was kept at 65—70° for 20 minutes a precipitate of octahydrorottlerone separated, and on isolation this product formed yellow prisms, m. p. 171°, from warm acetone containing a little acetic acid, identical with a specimen from natural sources.

Tetrahydroallorottlerin.—When concentrated sulphuric acid (0·5 c.c.) was added dropwise to a well-stirred solution of 5 : 7-dihydroxy-6-β-phenylpropionyl-2 : 2-dimethylchroman (Part III, *loc. cit.*) (0·16 g.) and *C*-methylphloroacetophenone (0·1 g.) in alcohol (6 c.c.), containing 40% aqueous formaldehyde

* In view of the conclusive evidence now available regarding the chemistry of rottlerin and its derivatives and for the sake of clarity we have now adopted the nomenclature suggested in a footnote to Part V (*loc. cit.*).

(1 c.c.), a yellow precipitate began to separate. Next day the product (0·25 g.) was collected, washed with water, dried, and extracted with warm acetone (5 c.c.). On cooling, the extract deposited tetrahydro-*allo*rottlerin (0·1 g.), m. p. 235—240°, which on recrystallisation from alcohol formed long, slender, bright yellow prisms (0·05 g.), m. p. 241°, alone or mixed with a natural specimen with which it was identical in every way (Found: C, 69·3; H, 6·0. Calc. for $C_{20}H_{22}O_8$: C, 69·2; H, 6·2%). On being kept the acetone filtrate from the crude tetrahydro*allo*rottlerin slowly deposited crystals of a further quantity (small) of this material mixed with octahydro*allo*rottlerone which were separated manually. On purification from alcohol the latter compound had m. p. 174—175° and was identical with an authentic specimen.

Treatment of the synthetic tetrahydro*allo*rottlerin with warm 4% aqueous sodium hydroxide as described in Part V (*loc. cit.*) gave rise to octahydro*allo*rottlerone, m. p. and mixed m. p. 174—175°.

Rottlerone Change.—(*a*) A mixture of synthetic octahydrorottlerone (Part IV, *loc. cit.*) (1 g.), 2 : 4 : 6 : 2′ : 4′ : 6′-hexahydroxy-5 : 5′-diacetyl-3 : 3′-dimethyldiphenylmethane (*loc. cit.*) (0·7 g.), and acetic acid (140 c.c.) was refluxed (oil-bath at 140—145°) for 12 hours and, after having been filtered to remove the unchanged hexahydroxy-diphenylmethane, was treated with water (7 c.c.). Two days later the crystalline octahydrorottlerone (0·63 g.) which had separated was removed, the mixture was diluted with excess of water, and the resulting reddish precipitate (0·2 g.) was repeatedly crystallised from alcohol, giving tetrahydrorottlerin, m. p. 212°, identical in every way with an authentic specimen (Found: C, 69·4; H, 6·2%). The same result was obtained when a specimen of octahydrorottlerone from natural sources was used.

(*b*) Synthetic octahydro*allo*rottlerone (Part V, *loc. cit.*) (0·1 g.) and 2 : 4 : 6 : 2′ : 4′ : 6′-hexahydroxy-5 : 5-diacetyl-3 : 3′-dimethyldiphenylmethane (*loc. cit.*) (0·07 g.) were gently boiled with acetic acid (40 c.c.) for 12 hours and the hot mixture filtered to remove the unchanged hexahydroxydiphenylmethane. On being kept the solution gradually deposited a yellow solid consisting of tetrahydro*allo*rottlerin and unchanged octahydro*allo*rottlerone (0·065 g.). Extraction of the mixture with hot benzene removed octahydro*allo*rottlerone, and then repeated crystallisation of the residue from alcohol gave tetrahydro-*allo*rottlerin (0·004 g.), m. p. 240—241°, alone or mixed, with a natural specimen with which it was identical in every way. When the acetic acid filtrate from the crude mixture of tetrahydro*allo*rottlerin and octahydro*allo*rottlerone was diluted with twice its volume of water a precipitate separated which consisted mainly of octahydro*allo*rottlerone, m. p. 175°, after purification. The use of natural octahydro*allo*rottlerone gave identical results.

The authors are indebted to Messrs. Imperial Chemical Industries Ltd. for a grant in aid of this investigation.

THE UNIVERSITY OF LIVERPOOL. [*Received, February 15th*, 1947.]

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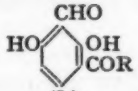
29. *Furano-compounds. Part VI. A Synthesis of Karanjic Acid.*

By REGINALD T. FOSTER and ALEXANDER ROBERTSON.

Cyclisation of the dibasic acid (II; R, R_1, and R_2 = H) gave rise to karanjic acid (III; R = OH) and its acetate. A synthesis of the ketone (III; R = CH_2·OMe) could not be effected by this route.

THE experiments described in the present communication, leading to a new direct synthesis of karanjic acid (III; R = OH) (cf. Limaye, *Rasayanam*, 1936, 14), an important degradation product of the furanoflavone, karanjin, were carried out in the course of studies on a complete synthesis of the latter compound. When it was found that the ketone (III; R = CH_2·OMe) required for the synthesis of the flavone could not be obtained by the application of the standard methods to karanjol it became clear that the most feasible route was by way of karanjic acid, a procedure which has since been described by Seshadri and Venkateswarlu (*Proc. Indian Acad. Sci.*, 1941, **13**, 404).



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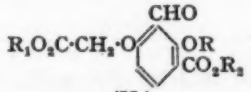

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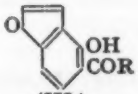

(III.)

Interaction of (I; R = OMe) with ethyl bromoacetate, in boiling acetone containing potassium carbonate, gave rise to (II; R = H, R_1 = Et, R_2 = Me) with smaller amounts of (II, R = CH_2·CO_2Et, R_1 = Et, R_2 = Me) which was unexpected in view of the resistance of similar compounds to complete alkylation by this method (*e.g.*, Curd and Robertson, *J.*, 1933, 437). When ethyl bromoacetate was replaced by benzyl bromide both *mono-* and *di-benzyl ethers* were formed. On being heated with acetic anhydride and sodium acetate the dibasic *acid* (II; R, R_1, and R_2 = H) formed by the hydrolysis of (II; R = H, R_1 = Et, R_2 = Me) was converted into a mixture of O-*acetylkaranjic acid* and karanjic acid (III; R = OH), identical with the natural material. It was found that this procedure for the production of

karanjic acid could not be applied to the direct synthesis of the ketone (III; R = CH_2·OMe) from (I; R = CH_2·OMe) because the latter was not formed from ω-methoxyresacetophenone by Gattermann's method although under the same conditions resacetophenone gives good yields of (I; R = Me) (cf. Shah and Shah, *J.*, 1939, 133).

Experimental.

Benzylation of 2 : 6-dihydroxy-3-carbomethoxybenzaldehyde (Shah and Laiwalla, *J.*, 1938, 1828) 3 g.) with benzyl bromide (2·5 g.; 1·3 mols.) and potassium carbonate (5 g.) in boiling acetone for 4 hours gave a mixed product which, by means of ether and dilute aqueous sodium hydroxide, was separated into 2-*hydroxy*-3-*carbomethoxy*-6-*benzyloxy*- and 3-*carbomethoxy*-2 : 6-*dibenzyloxy-benzaldehyde*. The monobenzyl ether separated from alcohol in needles (0·5 g.), m. p. 118°, having a dark red ferric reaction in alcohol (Found : C, 66·9; H, 4·8. $C_{16}H_{14}O_5$ requires C, 67·1; H, 4·9%) and gave a 2 : 4-*dinitrophenylhydrazone*, forming orange needles, m. p. 230°, from ethyl acetate (Found : N, 12·2. $C_{22}H_{18}O_8N_4$ requires N, 12·0%). On hydrolysis with dilute aqueous sodium hydroxide this ether gave 2-*hydroxy*-3-*carboxy*-6-*benzyloxybenzaldehyde*, forming clusters of needles, m. p. 168°, from aqueous acetone (Found : C, 66·2; H, 4·5. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%).

Crystallised from ethyl acetate, the dibenzyl ether was obtained in elongated prisms (0·5 g.), m. p. 105°, having a negative ferric reaction (Found : C, 73·7; H, 5·4. $C_{23}H_{20}O_5$ requires C, 73·4; H, 5·3%); it gave a 2 : 4-*dinitrophenylhydrazone*, forming clusters of orange-red needles, m. p. 185°, from ethyl acetate (Found : N, 10·3. $C_{29}H_{24}O_8N_4$ requires N, 10·1%).

The solid potassium salts remaining after the filtration of the acetone solution of the mixed product gave unchanged 2 : 6-dihydroxy-3-carbomethoxybenzaldehyde (1·8 g.) on treatment with dilute hydrochloric acid.

3-*Hydroxy*-2-*formyl*-4-*carboxyphenoxyacetic Acid* (II; R, R_1, and R_2 = H).—A mixture of 2 : 6-dihydroxy-3-carbomethoxybenzaldehyde (3 g.), ethyl bromoacetate (2 ml.; 1·1 mols.), potassium carbonate (6 g.), and acetone (200 ml.) was refluxed for 6 hours and the acetone containing a flocculent yellow product was decanted from the potassium salts. On being treated with dilute hydrochloric acid this yellow solid gave *ethyl* 3-*hydroxy*-2-*formyl*-4-*carbomethoxyphenoxyacetate* (II; R = H, R_1 = Et, R_2 = Me) which formed elongated rectangular prisms (2 g.), m. p. 87°, from aqueous acetone, having a violet red ferric reaction in alcohol (Found : C, 55·4; H, 4·9. $C_{13}H_{14}O_7$ requires C, 55·3; H, 5·0%). The 2 : 4-*dinitrophenylhydrazone* separated from alcohol in clusters of orange needles, m. p. 195° (Found : N, 12·3. $C_{19}H_{18}O_{10}N_4$ requires N, 12·1%). Hydrolysis of this ester (2 g.) with 4% aqueous sodium hydroxide (30 ml.) on the steam-bath for 5 minutes gave the dibasic *acid* which separated from water in small glistening plates (1·6 g.), m. p. 240° (decomp.), having a dark red ferric reaction in alcohol (Found : C, 50·0; H, 3·5. $C_{10}H_8O_7$ requires C, 50·0; H, 3·3%).

Concentration of the acetone filtrate from the flocculent solid left a viscous oil which did not solidify. A solution of this in ether was washed with dilute sodium hydroxide, dried, and evaporated, leaving an oil which did not give a ferric reaction, appeared to be mainly (II; R = CH_2·CO_2Et, R_1 = Et, R_2 = Me), and was characterised by the formation of a 2 : 4-*dinitrophenylhydrazone*, forming clusters of orange needles, m. p. 168°, from alcohol (Found : C, 50·0; H, 4·4; N, 10·4. $C_{23}H_{24}O_{12}N_4$ requires C, 50·4; H, 4·4; N, 10·2%).

Karanjic Acid (III; R = OH).—A mixture of the acid (II; R,R_1, and R_2 = H) (8 g.), acetic anhydride (80 ml.), and sodium acetate (20 g.) was refluxed for 1·5 hours and treated with excess of water. Next day a small amount of brown solid was removed by filtration and the liquid treated with sodium hydrogen carbonate (80 g.) and repeatedly extracted with ether. Evaporation of the combined dried extracts left a mixture of karanjic acid and its *acetate* which were separated by trituration with cold alcohol. Crystallisation of the residual solid from aqueous acetic acid gave the acetate in colourless, elongated prisms (1 g.), m. p. 173°, having a negative ferric reaction (Found : C, 60·1; H, 3·7. $C_{11}H_8O_5$ requires C, 60·0; H, 3·6%). Concentration of the alcoholic washings of the acetate yielded karanjic acid which formed colourless rectangular prisms (2 g.), m. p. 218° (decomp.), from aqueous alcohol, having a blue ferric reaction, identical with a specimen obtained by hydrolysis of the acetate (Found : C, 60·9; H, 3·4. Calc. for $C_9H_8O_4$: C, 60·7; H, 3·4%).

The authors are indebted to Messrs. Imperial Chemical Industries Limited for a grant in aid of this investigation.

University of Liverpool. [*Received, February 24th*, 1947.]

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30. *The Oxidation Products of Phenols. Part I. The Structure of Purpurogallin.*

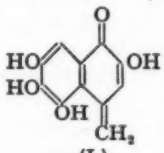
By J. A. Barltrop and J. S. Nicholson.

The evidence bearing on the structure of purpurogallin, an oxidation product of pyrogallol, is summarised, and a new structure (III), containing a seven-membered tropolone ring, is advanced. The isolation of trimethoxyphthalic anhydride as a degradation product of tetramethyl purpurogallin completely refutes Willstätter's structure (II). The relation between (III) and colchicine is emphasised.

The fact that a number of complex naturally occurring substances can be theoretically derived from relatively simple phenolic residues by oxidative coupling, *i.e.*, by a union of the phenolic

nuclei involving loss of hydrogen atoms, has led us to institute a series of researches into the oxidation products of phenols. Previous work in this field has been carried out mainly by Dianin (*Ber.*, 1873, **6**, 1252), Tiemann (*Ber.*, 1885, **18**, 3493), Cousin and Herissey (*Bull. Soc. chim.*, 1908, **3**, 1066, 1070), Pummerer *et al.* (*Ber.*, 1914, **47**, 1472, 2957; 1919, **52**, 1403, 1414; 1922, **55**, 3116; 1925, **58**, 1808; 1926, **59**, 2161), Erdtmann (*Svensk Kem. Tids.*, 1934, **46**, 226), Perkin *et al.* (*J.*, 1905, **87**, 1412; 1903, **83**, 192; 1908, **93**, 1186), and Haworth and Cartwright (*J.*, 1944, 535).

This paper is concerned with the structure of purpurogallin, a substance $C_{11}H_8O_5$, obtained from pyrogallol on oxidation, electrolytically, or with a variety of reagents, *e.g.*, sodium iodate, nitrous acid, silver ions, potassium permanganate and benzoquinone. Glucosides of purpurogallin occur naturally as the colouring matters of many galls (Nierenstein and Swanton, *Biochem. J.*, 1944, **38**, 373).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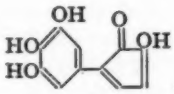
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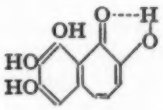
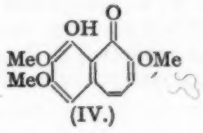

(III.)

Two structures have hitherto been advanced, a methylene-quinone structure (I) due to Dean and Nierenstein (*Ber.*, 1913, **46**, 3868), and a trihydroxyphenyl*cyclo*pentadienolone (II) due to Willstätter and Heiss (*Annalen*, 1923, **433**, 17). It is the purpose of this communication to advance a third structure (III) containing a seven-membered ring.

The properties of purpurogallin are recorded in papers by Perkin *et al.* (*locc. cit.*; *J.*, 1904, **85**, 243; 1906, **89**, 802; 1912, **101**, 803), Nierenstein and his co-workers (*Ber.*, 1913, **46**, 3151, 3868), and Herzig (*Annalen*, 1923, **432**, 99). It is a brick-red solid very sparingly soluble in most solvents, which on shaking with air in alkaline solution gives an intensely blue substance. It contains four hydroxyl groups, giving a tetra-acetyl derivative. With diazomethane an orange-yellow trimethyl purpurogallin is obtained, which on treatment with hot methyl sulphate and alkali affords a colourless tetramethyl purpurogallin. On the basis of structure (III) for purpurogallin the trimethyl ether would be (IV).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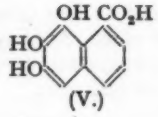
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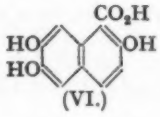
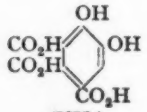

(VI.)

Other facts having a bearing on the structure are: (i) Bromine is not added to purpurogallin, but is substituted in it to form a dibromo-derivative. (ii) Purpurogallin is stable to Clemmensen reduction (Herzig, *loc. cit.*): this is very difficult to explain on either structure (I) or (II). (iii) Purpurogallin is stable to alcoholic hydrogen chloride in a sealed tube at 150°. One would expect the αβ-unsaturated ketone linkage of (II) to add hydrogen chloride under these conditions. Also methylene-quinones are extremely reactive systems (see Lindemann, *Annalen*, 1923, **431**, 270; Bistrzycki and Herbst, *Ber.*, 1903, **36**, 2333), with very strongly developed tendencies to add reagents of the type HX to afford the more stable aromatic *p*-hydroxybenzyl derivatives. The stability of purpurogallin to alcoholic hydrogen chloride is not explicable on the formulation (I). In addition, it possesses none of the properties of methylene-quinones, such as very facile hydration. (iv) Purpurogallin shows no ketonic properties. Nierenstein and Spiers's claim (*Ber.*, 1930, **46**, 3151) that tetra-acetyl purpurogallin forms a phenylhydrazone is incorrect (Herzig, *loc. cit.*), and we were unable to form a 2 : 4-dinitrophenylhydrazone from the parent substance. (v) Purpurogallin, on being heated to 170° with concentrated potassium hydroxide solution, is transformed into an isomer, purpurogallone, $C_{11}H_8O_5$, and *iso*purpurogallone, $C_{22}H_{14}O_{10}$, an oxidation product of purpurogallone. Purpurogallone has been suggested by Perkin (*J.*, 1912, **101**, 803) to be (V)—the alternative structure (VI) proposed by him is very improbable.

It should be emphasised that very little reliance can be placed in the degradations of purpurogallin reported by Dean and Nierenstein (*loc. cit.*). Although 34 years have elapsed since these authors claimed the isolation of trimethoxyphthalonic acid from trimethyl purpurogallin by hydrogen peroxide oxidation, and promised further details of its properties, no

further communication has appeared. Further, their degradation of purpurogallin by nitric acid to dihydroxyhemimellitic acid (VII) could not be repeated either by Herzig or by us. Indeed, as Herzig points out, the properties of the substance are so remarkable and so similar to those of oxalic acid, which was the only substance isolated by us, that there is considerable doubt whether they ever obtained it. The experimental support for structure (I) is thus



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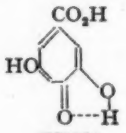

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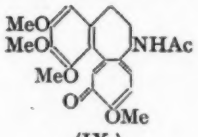


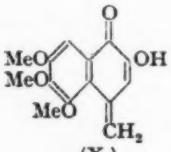
(IX.)

extremely scanty, if not non-existent, and the structure (II) not only does not adequately account for all the properties of purpurogallin, but is quite impossible in view of the oxidation of tetramethyl purpurogallin to trimethoxyphthalic anhydride described below.

It is our belief that the structure (III) is more consistent with the properties of the substance. Although it has not been definitely proved, there is evidence that *cyclo*heptatrienolone or tropolone rings occur in other natural products, *e.g.*, stipitatic acid (VIII) (Dewar, *Nature*, **1945**, **155**, 50) and colchicine (IX) (*idem*, *ibid.*, p. 141). There is a close parallel between stipitatic acid and purpurogallin. Neither shows ketonic properties, both are substituted by bromine, and both on heating with concentrated alkali are rearranged to an isomeric substance containing an extra carboxyl group.

If Dewar's suggestion (*loc. cit.*) is correct, then the tropolone ring is a new type of resonating *aromatic* system. Further, if purpurogallin contains a tropolone ring, then the facts (i)—(iv) find a ready explanation. As a resonance-stabilised aromatic molecule, the double bond and ketonic function would be masked, and thus substitutive attack by bromine, resistance to reduction by the Clemmensen method, stability to alcoholic hydrogen chloride, and lack of ketonic properties would be expected. The purpurogallone rearrangement would arise from the latent α-diketone grouping, under the drastic conditions involved, undergoing a benzilic acid rearrangement followed by dehydration; an α-naphthoic acid being thereby produced.

Having been led by the above theoretical considerations to the structure (III) for purpurogallin, we endeavoured to establish it by degradative experiments. Nierenstein and Swanton (*loc. cit.*, p. 374) baldly state that trimethyl purpurogallin is the 2 : 3 : 4-trimethyl derivative (X), although as far as is known no evidence has ever been published showing that the three methoxyl groups are all in the benzene ring. If they were, then trimethyl purpurogallin on hydrogenation should give a hexahydro-compound of structure (XI), the alicyclic ring of which could be degraded to establish its size and nature.



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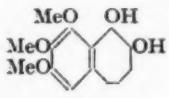

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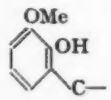


(XII.)

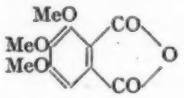
For this purpose, purpurogallin was prepared by oxidising pyrogallol with sodium nitrite and acetic acid, and by the much more convenient method of Evans and Dehn (*J. Amer. Chem. Soc.*, **1930**, **52**, 3647) involving sodium iodate. This was methylated with sodium hydroxide and methyl sulphate. Perkin and Stevens (*J.*, **1903**, **83**, 192) by using this procedure obtained trimethyl purpurogallin in only 10% yield, but in our hands this method has been improved to give 66% yields.

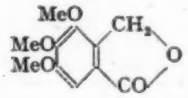
Hydrogenation of a suspension of the trimethyl ether in ethanol over Raney nickel or platinum oxide gave a *trimethyl hexahydropurpurogallin*, m. p. 147—148°. On one occasion, when only a small amount of platinum oxide catalyst was used, the hydrogenation proceeded very slowly, and only a yellow *trimethyl tetrahydropurpurogallin* could be isolated. The colour could not be removed by any crystallisation procedure, but it was subsequently found that if the compound was extensively hydrogenated over platinum oxide, a colourless specimen could be recovered. Attempts to relate the tetrahydro-derivative to the above hexahydro-trimethyl ether by hydrogenation were unsuccessful—even when 4 atoms of hydrogen had been absorbed, much unchanged tetrahydro-compound was recovered, and no other compound was isolable

from the reaction mixture, except on one occasion when a very small quantity of colourless solid, m. p. 148°, was obtained, but this depressed the m. p. of the hexahydro-compound. Both trimethyl tetra- and hexa-hydropurpurogallin are soluble in aqueous alkali and couple with *p*-nitrobenzenediazonium chloride. They are thus phenolic and this completely excludes (XI) for the hexa-hydro-compound. Confirmation of this was obtained by periodate oxidation, from which only a negligible amount of a non-homogeneous ketonic material was obtained. Further, sodium hypobromite, which has been used in the sterol series (Petrow and Starling, *J.*, 1946, 749) for conversion of α-glycols into carboxylic acids, gave no useful result—no positive evidence for the formation of a carboxylic acid could be obtained.

These results having cast some doubt on the hypothesis that the three methoxyl groups of trimethyl purpurogallin are all in the benzene ring, we felt that (IV) was a more plausible structure. Bearing in mind the marked steric hindrance associated with the phenolic grouping in systems of the type (XII), it became probable that the three methoxyl groups are distributed as shown, and, indeed, subsequent experiments showed that there was at least one phenolic grouping in the benzenoid ring.

Tetramethyl purpurogallin, obtained from the trimethyl compound with methyl sulphate and concentrated alkali, must necessarily possess three methoxyl groups in the benzene ring, and this was subjected to an oxidative degradation with potassium permanganate in aqueous acetone at room temperature. From the reaction mixture trimethoxyphthalic anhydride (XIII) was isolated by distillation, and found to be identical with a specimen prepared by the following

(XIII.) 

 (XIV.)

route. Trimethyl gallic acid was condensed with formaldehyde and hydrochloric acid to give a product containing chlorine—probably a crude chloromethyl derivative—which on treatment with potassium hydroxide yielded trimethoxyphthalide (XIV) previously prepared by Feist and Dschu (*Zentr.*, 1927, II, 58). This on oxidation with alkaline potassium permanganate gave (XIII). The isolation of this material as a degradation product at once disposes of Willstätter's structure (II) and lends support to the formulation (III). The Nierenstein structure (I) is also consistent with this piece of evidence but must be considered very improbable for the reasons previously advanced.

Trimethyl purpurogallin, when oxidised with potassium permanganate under conditions identical with those used for the tetramethyl ether, gave no trimethoxyphthalic anhydride. Much more permanganate was required to reach an end-point, and from the reaction mixture nothing could be isolated except oxalic acid and a trace of a high-melting yellow substance. There is therefore an unprotected phenolic group in the benzene ring of trimethyl purpurogallin, contrary to the statement of Nierenstein and Swanton, and their conclusions regarding the structure of eriophyesin are incorrect: the disaccharide residue must be located in the benzene ring.

There is a close structural relationship between (III) and colchicine (IX), and it may be significant that whereas colchicine is a mitosis poison, glucosides of purpurogallin are found in galls, *i.e.*, points of abnormal cell proliferation. Certain derivatives of purpurogallin have been synthesised and are being tested for their effect on cell division. This will be reported elsewhere.

Experimental.

Purpurogallin.—This was prepared according to Evans and Dehn (*loc. cit.*) in 72% yield. After crystallisation from glacial acetic acid it had m. p. 271—272° (Willstätter and Heiss give m. p. 272—273·5°, and Perkin m. p. 274—275°). Carrying out the reaction in an inert atmosphere effected no improvement in either the quality or the quantity of the product. Excess of iodate is to be avoided.

Trimethyl Purpurogallin.—A solution of sodium hydroxide (1·4 g.) in water (10 c.c.) was added to a mixture of purpurogallin (2·2 g.), methyl sulphate (3 c.c.), and ice (5 g.), and the whole shaken overnight in a stoppered bottle. The trimethyl ether (1·75 g.; 66%) was collected, washed with water, and crystallised from a large volume of ethanol (charcoal). The trimethyl purpurogallin had m. p. 170° (Perkin gives m. p. 174—177°) and was pure enough for subsequent operations.

Hydrogenation of Trimethyl Purpurogallin.—(A) Trimethyl purpurogallin (2 g.), suspended in ethanol (10 c.c.), was hydrogenated over Raney nickel catalyst at 60° (initial pressure 80 atm.) until 6 atoms of hydrogen had been absorbed. The catalyst was filtered off, and the solution concentrated to small bulk. *Trimethylhexahydropurpurogallin* (1 g.) crystallised. It recrystallised from xylene in colourless crystals, m. p. 147—148° (Found: C, 62·3; H, 7·3. $C_{14}H_{20}O_5$ requires C, 62·7; H, 7·5%). On occasion, only a gum was obtained on concentrating the ethanol solution, but trituration under ether induced crystallisation. An identical product could be obtained by hydrogenation over platinum oxide catalyst

at room temperature and pressure. The hexahydro-compound gives no ferric chloride coloration, but is soluble in aqueous alkali and couples with diazotised *p*-nitroaniline to give a red dye.

(B) Trimethyl purpurogallin (14 g.), suspended in ethanol (400 c.c.), was hydrogenated over platinum oxide catalyst (*ca.* 0·1 g.) at 60° and 1 atm. Hydrogen uptake was very slow. After 3 days, when the trimethyl ether had nearly all dissolved and the rate of hydrogenation was infinitesimal, the catalyst and unchanged trimethyl ether were filtered off, and the alcoholic solution evaporated under reduced pressure. The residual gum was dissolved in a small quantity of ethanol, and on standing deposited a little impure trimethyl ether, which was filtered off. On concentration to small bulk and standing, yellow needles, m. p. 78°, were slowly deposited. These were collected and washed with a little cold ethanol. After recrystallisation from water, *trimethyl tetrahydropurpurogallin* formed pale yellow needles, m. p. 80° (Found: C, 63·2, 63·1; H, 6·7, 6·7; active H, 0·4; *M*, 278. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8; 1 active H, 0·38%; *M*, 266). Light absorption in MeOH: Maxima, <2200 and 2880 A.; ε> 16,350 and 16,350. The tetrahydro-compound gave a reddish-purple ferric chloride reaction, dissolved in aqueous alkali, and coupled with *p*-nitrobenzenediazonium chloride to give a red dye.

Tetramethyl Purpurogallin.—The trimethyl ether (1·0 g.) on methylation with methyl sulphate and potassium hydroxide according to Willstätter and Heiss (*loc. cit.*) gave the tetramethyl ether (0·5 g.), m. p. 91—92°. This was recrystallised twice from methanol, once from aqueous methanol, and finally from ligroin (b. p. 80—100°), from which it separated in long, colourless rhomboids, m. p. 92° (Found: C, 65·1; H, 5·9. Calc. for $C_{15}H_{16}O_5$: C, 65·2; H, 5·8%).

Oxidation of the tetramethyl ether. To a solution of the above highly purified ether (0·15 g.) in purified acetone (5 c.c.) was slowly added, with intermittent shaking, a 2% aqueous solution of potassium permanganate (35 c.c.). The manganese dioxide was dissolved by use of sulphur dioxide, and the solution made alkaline, and concentrated to small bulk under reduced pressure. After being strongly acidified with concentrated hydrochloric acid, and exhaustively extracted with ether, the reaction products were isolated by distillation in bulbs. Trimethoxyphthalic anhydride (25 mg.), collected at 156—160° (bath)/0·03 mm., had m. p. 137°, undepressed by an authentic specimen (m. p. 140°) (Found: C, 55·5; H, 4·35. Calc. for $C_{11}H_{10}O_6$: C, 55·5, H, 4·2%). After recrystallisation from absolute ether, the anhydride was obtained with excellent recovery as colourless needles, m. p. 144°, undepressed on admixture with an authentic specimen.

Repetition of the experiment with tetramethyl purpurogallin (0·8 g.) gave the crude anhydride (0·2 g.), m. p. 134—137°.

Trimethoxyphthalide.—Trimethyl gallic acid (5 g.) was heated on the steam-bath for 30 mins. with aqueous formaldehyde (12 c.c. of 33%) and concentrated hydrochloric acid (20 c.c.). A dark oil separated and after being poured into water slowly solidified. This, after crystallisation from methanol, gave a colourless solid melting over a wide range, and which on boiling under reflux for 15 mins. with an excess of 65% potassium hydroxide solution and acidification with concentrated hydrochloric acid gave trimethoxyphthalide, m. p. 128°, raised by two crystallisations from methanol to 133° (Found: C, 58·5; H, 5·5. Calc. for $C_{11}H_{12}O_5$: C, 58·9; H, 5·4%). Feist and Dschu (*loc. cit.*) give m. p. 134°.

Trimethoxyphthalic Anhydride.—The above phthalide was oxidised with alkaline permanganate according to Feist and Dschu (*loc. cit.*). The anhydride formed fine needles, m. p. 140°.

Oxidation of Trimethyl Purpurogallin.—The ether (0·3 g.), dissolved in acetone (60 c.c.) which had been distilled over potassium permanganate, was oxidised during several days with portions of 2% aqueous potassium permanganate until a permanent pink colour developed (100 c.c. required). The oxidation products were isolated as in the oxidation of tetramethyl purpurogallin and distilled in bulbs at 0·1 mm. Fraction 1, collected at 60° (bath), was a colourless liquid crystallising on cooling. Fraction 2, a colourless crystalline solid was collected at 80—100° (bath), and fraction 3, a yellow solid, at 180°. Fractions 1 and 2 had properties consistent with their being methyl oxalate and oxalic acid respectively. Fraction 3 was a yellow solid, m. p. 202° (decomp.), which will be investigated further. No evidence for the formation of trimethoxyphthalic anhydride could be found.

The authors wish to thank Sir Robert Robinson for his encouragement and advice.

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31. *The Structure of Egg-plum Gum. Part II. The Hydrolysis Products obtained from the Methylated Degraded Gum.*

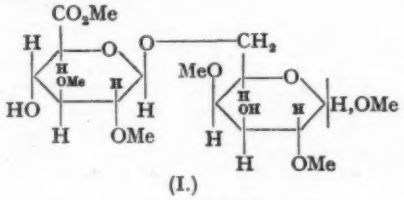
By E. L. HIRST and J. K. N. JONES.

Methylated degraded egg-plum gum has been hydrolysed and the following sugars identified amongst the products of hydrolysis: (*a*) 2 : 3 : 4 : 6-tetramethyl *d*-galactose, (*b*) 2 : 4 : 6-trimethyl *d*-galactose, (*c*) 2 : 3 : 4-trimethyl *d*-galactose, (*d*) 2 : 4-dimethyl *d*-galactose and 2 : 3-dimethyl *d*-glucuronic acid. A partly methylated aldobionic acid, 6-(2 : 3-dimethyl *d*-glucuronosido) 2 : 4-dimethyl *d*-galactose was also present amongst the products of hydrolysis.

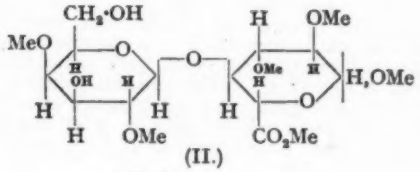
THE sugar residues present in egg-plum gum have been identified after hydrolysis with dilute aqueous acid as *l*-arabinose, *d*-xylose, *d*-galactose, and *d*-glucuronic acid, which occur respectively in the approximate proportions 3 : 1 : 3 : 1 (Part I, *J.*, 1947, 1064). No evidence as to the mode of linkage of these residues has been available with the important exception that a part at least of the glucuronic acid is known to be combined with galactose and appears after hydrolysis as the aldobionic acid 6-*d*-glucuronosido-*d*-galactose identical with the aldobionic acid obtainable

from gum arabic. The arabinose residues are extremely susceptible to acid hydrolysis and can be detached readily from the gum molecule. The xylose comes away less easily but can be removed almost completely from the gum without dislocation of its main chain structure. Further insight into the structure of the stable portion of the gum molecule is derivable from a study of the hydrolysis products obtained from the methylated derivative of the degraded gum. After separation of the products by fractional distillation, the following sugars were identified; (*a*) 2 : 3 : 4 : 6-tetramethyl *d*-galactose, recognised as its crystalline anilide and as the crystalline phenylhydrazide of 2 : 3 : 4 : 6-tetramethyl *d*-galactonic acid, (*b*) 2 : 4 : 6-trimethyl *d*-galactose, recognised as its crystalline anilide, (*c*) 2 : 3 : 4-trimethyl *d*-galactose, identified as its crystalline anilide and as the crystalline phenylhydrazide of 2 : 3 : 4-trimethyl *d*-galactonic acid, and (*d*) 2 : 4-dimethyl *d*-galactose, recognised as its crystalline anilide and as the phenylhydrazide of 2 : 4-dimethyl *d*-galactonic acid. The uronic acid portion consisted mainly of 2 : 3-dimethyl *d*-glucuronic acid, identified as the methyl ester of 2 : 3-dimethyl *d*-saccharolactone. No 2 : 3 : 4-trimethyl *d*-glucuronic acid could be detected. The degraded polysaccharide is therefore not identical structurally with the degraded polysaccharide obtained from gum arabic, although on hydrolysis both these degraded gums give glucuronic acid (1 part) and galactose (3 parts) (see Smith, *J.*, 1939, 1724).

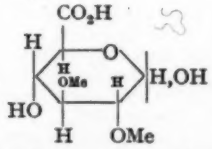
Some of the partly methylated glucuronic acid was found to be present as a disaccharide (I) which on hydrolysis gave a partly methylated derivative of *d*-glucuronic acid and a partly methylated derivative of *d*-galactose. These products, identified as 2 : 3-dimethyl *d*-glucuronic acid (III) and 2 : 4-dimethyl *d*-galactose (IV) may have been combined with one another either through the reducing group of the galactose molecule (formula II) or through the reducing group of the glucuronic acid molecule (formula I). The latter possibility is considered to be the more likely since the part of the gum molecule more resistant to hydrolysis is an aldobionic acid, 6-*d*-glucuronosido-*d*-galactose, which may be isolated from the products obtained after prolonged hydrolysis of the gum.



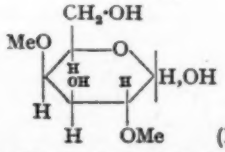
(I.)



(II.)



(III.)



(IV.)

If the methylated disaccharide is a derivative of this aldobionic acid it follows that in the degraded gum there are *d*-galactose units linked through their reducing groups to C_4 of the glucuronic acid residues and also *d*-galactose units linked glycosidically to C_3 of those *d*-galactose residues which occur in the aldobionic acid. At this stage, the presence of small quantities of other differently constituted aldobionic acids in the gum molecule cannot be ruled out.

Indications of the presence of small amounts of 2 : 3 : 4-trimethyl *d*-xylose in the 2 : 3 : 4 : 6-tetramethyl *d*-galactose fraction were obtained from an examination of the change in optical rotation of the sugar glycosides on hydrolysis. It is assumed that this material arises from the small amounts of *d*-xylose which remained in the degraded gum molecule, during the removal of the *l*-arabinose residues, owing to the greater resistance of *d*-xylopyranose to hydrolysis.

A satisfactory quantitative estimation of the sugars present in the methylated degraded gum molecule could not be made from an examination of the yields of sugars and of their anilides owing to the complex nature of the mixture obtained on hydrolysis, but it is evident that the degraded polysaccharide is composed of the following residues linked through the carbon atoms indicated.

$$\text{Ga,1,}\ldots\ \ldots 6,\text{Ga,1,}\ldots\ \ldots 3,\text{Ga,1,}\ldots\ \ldots \overset{\vdots}{\underset{3}{6}},\text{Ga,1,}\ldots\ \ldots 4,\text{Glu,1,}\ldots\ \ldots \overset{\vdots}{\underset{3,}{4}},\text{Glu,1,6,Ga,1,}\ldots$$

Where Ga = *d*-galactopyranose residue and Glu = *d*-glucuronic residue.

It will be observed that *d*-galactose is the major component of the degraded gum and that the -1 : 3- and -1 : 6-linkages are again encountered as in the main chain of gum arabic, damson gum, and cherry gum. The galactose residues all occur in the pyranose form and therefore cannot be the direct precursors of the *l*-arabofuranose residues present in the undegraded gum molecule.

Experimental.

The degraded arabinose-free polysaccharide (15·6 g.) was dissolved in thallous hydroxide (300 c.c.; N) and evaporated under reduced pressure at 40° to a solid which was ground to a powder (fume cupboard—use rubber gloves). The solid was boiled under reflux with methyl iodide until the solid reacted neutral to litmus (24 hours). Excess of methyl iodide was distilled off and the residue extracted with methyl alcohol and then with aqueous alcohol. The combined extracts were evaporated to dryness (40°, 12 mm.) and the residue (14·5 g.) was dissolved in aqueous alcohol (50 c.c.), and thallous ethoxide in benzene (150 c.c.; N) added. The solution was evaporated to dryness and the residual solid powdered (observing the usual precautions) and boiled with methyl iodide. After 24 hours, excess of methyl iodide was boiled off and the residual solid exhaustively extracted with acetone. Concentration of the extracts gave the crude methylated polysaccharide (14·5 g.; OMe, 43·7%) which was purified by dissolving in methyl iodide and boiling with silver oxide. The methylated polysaccharide (13·5 g.; OMe, 43·9%) was isolated as a crisp cream-coloured solid. It was fractionated by dissolving in acetone (50 c.c.) followed by the gradual addition of ether. In this way, three fractions were isolated. Fraction I (2·3 g.), $[\alpha]_D^{20°}$ + 11° (*c*, 0·6 in methyl alcohol) (Found: OMe, 38·0%). Fraction II (9·7 g.), $[\alpha]_D^{20°}$ + 9° (c, 1·7 in methyl alcohol) (Found: OMe, 44·5%). Fraction III (1·5 g.), a sticky solid, not further examined. Fraction II was used in the experiments detailed below.

Hydrolysis of the Methylated Polysaccharide.—Fraction II (8·5 g.) was dissolved in sulphuric acid (50 c.c.; N) and heated at 90° for 48 hours. The substance, initially insoluble, gradually went into solution; it was not possible to observe any change of optical rotation owing to darkening of the solution. The cooled solution was neutralised with barium carbonate, filtered, and evaporated to dryness. The residue (a brown solid) was extracted with acetone; this removed sugars and the barium salts of some oligosaccharide since the acetone extract (A) gave a positive test for barium ions. The residual barium salts were dissolved in water, filtered, and concentrated to a dry solid (B) (2·0 g.) (Found: Ba, 20·3%).

The sugars (A) were boiled with 2·5% methyl-alcoholic hydrogen chloride (50 c.c.) for 25 hours. The mixture was then cooled, neutralised with silver carbonate, and the solution worked up in the usual manner. The resultant syrupy glycosides (7·0 g.) were boiled for 5 hours with excess of barium hydroxide, cooled, and the solution neutralised (phenolphthalein) with dilute sulphuric acid. The solution was concentrated in a vacuum at 40° to a syrup which was dissolved in water (30 c.c.) and extracted exhaustively with light petroleum (b. p. 40—60°). Concentration of the extract gave a syrup (C) (0·73 g.). The aqueous solution was then extracted exhaustively with ether which on concentration gave a further quantity of syrup (2·54 g.). The aqueous solution was then evaporated to dryness under reduced pressure at 40° and the solid extracted exhaustively with ether. Concentration of this extract gave a product (1·4 g.) which was combined with the fraction, 2·54 g. above, giving a fraction (D) (3·94 g.).

The residual barium salts from the ether extraction (3·2 g.) were combined with the fraction (B) and the solid (5·1 g.) was dissolved in 5% methyl-alcoholic hydrogen chloride (100 c.c.) and kept at 20° for 30 days. The solution was then neutralised with diazomethane and concentrated immediately under reduced pressure at 40°. The residual syrup (E) was isolated from the barium chloride by extraction with acetone–ether (1 : 1). The low yield (3·1 g.) probably indicates that some incompletely hydrolysed material had not been extracted from the barium chloride by the solvent used.

Examination of the Sugar Fractions (C) and (D).—Fraction (C) was distilled, and gave: Fraction (i) (0·28 g.), b. p. 100—105° (bath temp.)/0·01 mm., $n_D^{23°}$ 1·4492 (Found: OMe, 58·3%). Fraction (ii) (0·21 g.), b. p. 100—105° (bath temp.)/0·01 mm., $n_D^{23°}$ 1·4532 (Found: OMe, 53·4%). The residue (0·20 g.) was combined with Fraction (D) and distillation was continued. Fraction (iii) (0·58 g.), b. p. 110—120° (bath temp.)/0·01 mm., $n_D^{20°}$ 1·4570 (Found: OMe, 53·4%). Fraction (iv) (0·24 g.), b. p. 120—160° (bath temp.)/0·01 mm., $n_D^{20°}$ 1·4580 (Found: OMe, 52·5%). Fraction (v) (0·97 g.), b. p. 160° (bath temp.)/0·01 mm., $n_D^{20°}$ 1·4620 (Found: OMe, 49·8%). Fraction (vi) (0·72 g.), b. p. 160—170° (bath temp.)/0·01 mm., $n_D^{18°}$ 1·4710 (Found: OMe, 42·4%). Fraction (vii) (0·36 g.), b. p. 170—220° (bath temp.)/0·01 mm., $n_D^{18°}$ 1·4740 (Found: OMe, 40·7%). Residue (1·0 g.). Loss during distillation, 0·4 g. Fractions (i), (ii), and (iii) were combined (1·05 g.) and hydrolysed with N-hydrochloric acid (25 c.c.); $[\alpha]_D^{20°}$ + 76° (initial value), + 85° (1¼ hours), + 69° (constant value). The low equilbrium value indicated that galactose was not the only sugar present. The cooled solution was neutralised with silver carbonate, filtered, and concentrated under reduced pressure at 40°. The residual syrup (1·0 g.), $n_D^{23°}$ 1·4678, was fractionally distilled giving Fraction (viii) (0·47 g.), b. p. 160° (bath temp.)/0·01 mm., $n_D^{23°}$ 1·4678 (Found: OMe, 48·5%). Fraction (ix) (0·31 g.), b. p. 170° (bath temp.)/0·01 mm., $n_D^{24°}$ 1·4738 (Found: OMe, 43·0%). Residue (0·14 g.). Loss, 0·06 g. Fraction (viii), $[\alpha]_D^{20°}$ + 46° (*c*, 2·8 in ethyl alcohol) (230 mg.), was boiled with ethyl-alcoholic aniline for 2 hours, when it gave a mixture of 2 : 3 : 4 : 6-tetramethyl *d*-galactose anilide, m. p. 194° not depressed on admixture with an authentic specimen, and 2 : 4 : 6-trimethyl *d*-galactose anilide, m. p. and mixed m. p. with an authentic specimen 179°. The two materials were separated by fractional crystallisation from absolute alcohol and were present in the proportion of approximately 2 : 1 (80 mg. of tetra- and 40 mg. of tri-methyl galactose anilides were isolated). A portion of the sugar (0·2 g.) was oxidised with bromine water. The isolated lactones did not crystallise, and no crystalline amide could be prepared. A small quantity of a crystalline phenylhydrazide was isolated, however, m. p. 137°, not depressed on admixture with an authentic specimen of the phenylhydrazide of 2 : 3 : 4 : 6-tetramethyl *d*-galactonic acid. Fraction (ix), $[\alpha]_D^{20°}$ + 40° (*c* 1·8 in ethyl alcohol) (100 mg.), was boiled with ethyl-alcoholic aniline for 2 hours, when it

gave a mixture of 2 : 4 : 6-trimethyl *d*-galactose anilide, m. p. 179°, and 2 : 3 : 4-trimethyl *d*-galactose anilide, m. p. 169°, not depressed on admixture with the corresponding authentic anilides. A sample of the sugars, on oxidation with bromine water, gave a lactone which with alcoholic phenylhydrazine gave the phenylhydrazide of 2 : 3 : 4-trimethyl *d*-galactonic acid, m. p. 174°, not depressed on admixture with an authentic specimen. Fractions (iv) and (v) (1·17 g.) were hydrolysed with boiling N-hydrochloric acid (25 c.c.); $[\alpha]_D^{20°}$ + 90° ⟶ + 85° (constant value, 5 hours). The reducing sugar (1·07 g.) was isolated after neutralisation of the hydrolysis solution with silver carbonate; $[\alpha]_D^{20°}$ + 87° (*c*, 7·1 in water) (Found : OMe, 41·0%). The syrup (0·6 g.) on refluxing with alcoholic aniline gave a mixture of anilides from which 2 : 3 : 4-trimethyl *d*-galactose anilide (0·4 g.), m. p. 169°, and 2 : 4 : 6-trimethyl *d*-galactose anilide (0·1 g.), m. p. 179°, were isolated. The sugar (0·45 g.) on oxidation with bromine water gave a syrupy mixture of acid and lactone, $n_D^{18°}$ 1·4700, $[\alpha]_D^{20°}$ + 89° (*c*, 1·8 in water, initial value) falling to + 26° (constant value, 24 hours) (Found : Equiv., 248). A portion of the lactone on being heated with alcoholic phenylhydrazine gave the phenylhydrazide of 2 : 3 : 4-trimethyl *d*-galactonic acid, m. p. and mixed m. p. 175°, after recrystallisation from alcohol. Fraction (vi) (0·72 g.) was hydrolysed with boiling N-hydrochloric acid (25 c.c.); $[\alpha]_D^{20°}$ + 92° ⟶ + 84° (constant value, 7 hours). The sugar (0·66 g.) was isolated. No crystalline anilide could be obtained on refluxing a portion of the sugar with alcoholic aniline. On oxidation with bromine water the sugar gave a mixture of lactone and acid, $[\alpha]_D^{20°}$ + 45° (*c*, 1·04 in water, initial value) falling to + 25° (constant value, 24 hours) (Found : Equiv., 209). A portion of the lactone (300 mg.) on being heated with alcoholic phenylhydrazine gave the phenylhydrazide of 2 : 4-dimethyl *d*-galactonic acid (90 mg.), m. p. and mixed m. p. 183°. Fraction (vii) (0·36 g.) was hydrolysed with boiling N-hydrochloric acid (25 c.c.); $[\alpha]_D^{20°}$ + 87° (7 hours, constant value). The sugar (0·26 g.) on being boiled with alcoholic aniline gave the anilide of 2 : 4-dimethyl *d*-galactose (0·10 g.), m. p. 206°, not depressed on admixture with an authentic specimen.

Examination of the Uronic Acid Fraction.—A portion (2·38 g.) of the syrup (E) isolated from the barium salts (B) was distilled, giving Fraction (x) (0·64 g.), b. p. 130°/0·01 mm., $n_D^{15°}$ 1·4538, $[\alpha]_D^{20°}$ + 55° (*c*, 0·4 in water) (Found : Equiv., 244; OMe, 50·1%). Fraction (xi) (0·43 g.), b. p. 165°/0·01 mm., $n_D^{15°}$ 1·4788 (Found : OMe, 39·0%. The *methyl* ester of 6-[2·3 dimethyl-*d*-glucuronosido] 2 : 4-dimethyl-*d*-galactoside requires OMe, 40·2%). Fraction (xii) (0·80 g.), $n_D^{20°}$ 1·4808 (Found : OMe, 41·0%). The residue (0·36 g.) was not further examined. Fraction (x) (0·54 g.) was hydrolysed with boiling N-hydrochloric acid (25 c.c.); $[\alpha]_D^{20°}$ + 35° (initial value) ⟶ + 50° (constant value, 4 hours). The sugar was oxidised with bromine water after isolation. The resulting 2 : 3-dimethyl *d*-saccharic acid was esterified with boiling methyl-alcoholic hydrogen chloride, the solution filtered before and after neutralisation with silver carbonate, and the isolated product distilled in a vacuum giving the methyl ester of 2 : 3-dimethyl 1 : 4-*d*-saccharolactone (0·3 g.), m. p. 101°, not depressed on admixture with an authentic specimen. Fraction (xi) appeared to consist mainly of a disaccharide; accordingly the syrup (0·32 g.) was hydrolysed with boiling N-hydrochloric acid (25 c.c.) for 7 hours; $[\alpha]_D^{20°}$ + 52° (initial value) ⟶ + 44° (constant value, 7 hours). The solution was neutralised with silver carbonate and filtered, silver ions were removed with hydrogen sulphide, and the filtered solution was concentrated under reduced pressure at 40°. The concentrated solution was neutralised by titration with barium hydroxide and the neutral solution evaporated to dryness. Exhaustive extraction with acetone gave an acetone-insoluble fraction, (xi*a*) (0·2 g.), mainly the barium salt of 2 : 3-dimethyl *d*-glucuronic acid, an acetone-soluble (xi*b*) (0·1 g.), mainly 2 : 4-dimethyl *d*-galactose since this fraction on being boiled with alcoholic aniline gave 2 : 4-dimethyl *d*-galactose anilide, m. p. and mixed m. p. 208°. Fraction (xi*a*) was dissolved in water and oxidised with bromine water. The isolated product was esterified with methyl-alcoholic hydrogen chloride and the product (0·16 g.) distilled at 130°/0·01 mm. The distillate crystallised and had m. p. 100° after recrystallisation from ether, not depressed on admixture with an authentic specimen of methyl 2 : 3-dimethyl *d*-saccharolactone ester. Fraction (xii) had the constants of a disaccharide. Attempts to convert it into a crystalline *p*-nitrobenzoyl derivative were unsuccessful. Accordingly, the material (0·40 g.) was hydrolysed with N-hydrochloric acid (25 c.c.) for 7 hours ($[\alpha]_D$ not observable owing to the colour of the solution). The cooled solution was then neutralised with silver carbonate and filtered before and after the passage of hydrogen sulphide. The filtrate was concentrated (50 c.c.) and neutralised with barium carbonate, filtered, the filtrate evaporated to dryness in a vacuum, and the residue exhaustively extracted with acetone (J). The residual barium salts were oxidised with aqueous bromine and the resulting 2 : 3-dimethyl *d*-saccharic acid converted into the crystalline methyl 2 : 3-dimethyl *d*-saccharolactone ester (0·09 g., m. p. 101°) by the method described above. The acetone solution (J) on concentration gave a syrup (0·1 g.) from which no crystalline derivative could be isolated.

THE UNIVERSITY, MANCHESTER, 13. [*Received, March 3rd*, 1947.]

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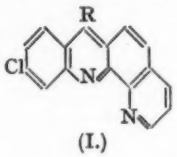
32. *Attempts to find New Antimalarials. Part XXVII. Derivatives of Various Benzacridines and Pyridoacridines.*

By JAMES DOBSON, WILLIAM C. HUTCHISON, and WILLIAM O. KERMACK.

In view of the pronounced antimalarial activity of derivatives of 3 : 4 : 2′ : 3′-pyridoacridine containing a chlorine atom in position 8 and a basic side chain in position 5 of the acridine nucleus, analogous derivatives have been prepared of 3 : 4-benzacridine and 3 : 4 : 3′ : 2′-pyridoacridine. The benzacridine derivative was active whilst the new pyridoacridine was only doubtfully so. Corresponding derivatives of 1 : 2-benzacridine and of 1 : 2 : 3′ : 2′-pyridoacridine have also been prepared, but these like the already known 1 : 2 : 2′ : 3′ pyridoacridine derivatives were without significant antimalarial activity.

In a previous paper (Dobson and Kermack, *J.*, 1946, 150) an account has been given of the preparation of derivatives of 1 : 2 : 2′ : 3′-pyridoacridine and 3 : 4 : 2′ : 3′-pyridoacridine carrying in position 5 of the acridine nucleus a basic side chain of the type present in mepacrine. It was reported that tests in chicks infected with *P. gallinaceum* had demonstrated that certain derivatives of 3 : 4 : 2′ : 3′-pyridoacridine such as 8-chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine (II, R = NH·$[CH_2]_3$·NEt_2) evinced considerable antimalarial activity in this test, but that the corresponding 1 : 2 : 2′ : 3′-pyridoacridine (I, R = NH·$[CH_2]_3$·NEt_2) was inactive. Evidently the position of the additional pyridine ring has a great effect on the antimalarial activity.

It seemed desirable in the light of these results to prepare the corresponding benzacridines. When this work was begun, no compounds of the type envisaged appeared to have been made,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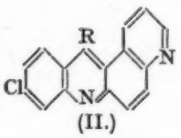
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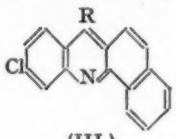
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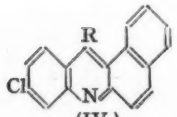
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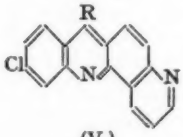
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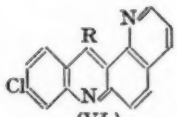
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but since its completion a paper has appeared by Bachman and Picha (*J. Amer. Chem. Soc.*, 1946, **68**, 1599) describing the synthesis of various benzacridines from α- and β-naphthylamine. Only three of our compounds happen to have been prepared by the American workers; these are derived from α-naphthylamine and 2 : 4-dichlorobenzoic acid. None of the bases prepared by Bachman and Picha possessed antimalarial activity.

As the chlorine atom in position 8 of the acridine nucleus appeared important, 2 : 4-dichlorobenzoic acid rather than *o*-chlorobenzoic acid was employed in our work. This acid was condensed with α-naphthylamine to yield 4-chloro-2-α-naphthylaminobenzoic acid which readily cyclised on boiling with phosphoryl chloride to 5 : 8-dichloro-1 : 2-benzacridine (III, R = Cl) (cf. Bachman and Picha, *loc. cit.*). A similar series of reactions starting from β-naphthylamine and 2 : 4-dichlorobenzoic acid gave 4-*chloro*-2-β-*naphthylaminobenzoic acid* and 5 : 8-*dichloro*-3 : 4-*benzacridine* (IV, R = Cl). The condensation of the two dichlorobenzacridines with diethylaminoalkylamines was carried out in phenol solution, and in this way the two bases, 8-*chloro*-5-(γ-*diethylaminopropylamino*)-1 : 2-*benzacridine* (III, R = NH·$[CH_2]_3$·NEt_2) and 8-*chloro*-5-(δ-*diethylamino*-α-*methylbutylamino*)-3 : 4-*benzacridine* (IV, R = NH·CHMe·$[CH_2]_3$·NEt_2) were obtained.

As shown in the table of biological results given below, the 3 : 4-benzacridine derivative was active, whilst the representative of the 1 : 2-benzacridine series was without antimalarial activity. This latter result agrees with that reported by Bachman and Picha (*loc. cit.*). It appeared that the position in which the extra ring was fused on was of greater importance than the nature of the ring whether pyridine or benzene.

It seemed that further useful information on the relation between structure and chemotherapeutic action in this group of compounds might be obtained by the preparation and biological testing of suitable derivatives of 1 : 2 : 3′ : 2′-pyridoacridine and 3 : 4 : 3′ : 2′-pyridoacridine. The simplest route for synthesising these appeared to be from 5- and 7-aminoquinoline respectively. The synthesis of 8-*chloro*-5-(γ-*diethylaminopropylamino*)-1 : 2 : 3′ : 2′-*pyridoacridine* (V, R = NH·$[CH_2]_3$·NEt_2) from 5-aminoquinoline and 2 : 4-dichlorobenzoic acid went smoothly through 4-*chloro*-5′-*quinolylanthranilic acid* and 5 : 8-*dichloro*-1 : 2 : 3′ : 2′-*pyridoacridine* (V, R = Cl), the condensation of the latter compound with γ-diethylaminopropylamine yielding the crystalline base. From 7-aminoquinoline and 2 : 4-dichlorobenzoic acid, 4-chloro-7′-quinolylanthranilic acid, purified as its *ethyl* ester, was obtained, and cyclised with phosphoryl chloride containing phosphorus pentachloride to 5 : 8-dichloro-3 : 4 : 3′ : 2′-pyridoacridine. The product, which after repeated crystallisations contained some admixed 8-chloro-3 : 4 : 3′ : 2′-pyridoacridone, was condensed with γ-diethylaminopropylamine to yield a product which separated from ligroin as an apparently homogeneous crystalline base, m. p. 99—100°, but was shown on analysis to possess the composition $3C_{23}H_{25}N_4Cl,C_{16}H_9ON_2Cl,3H_2O$.

This product lost water on drying over anhydrone under reduced pressure at room temperature. When the dried product was recrystallised several times from dry heptane, a crystalline *base*, m. p. 69—70°, was obtained, which analysed in accordance with the formula $C_{22}H_{25}N_4Cl,H_2O$. It must be assumed that this compound has a high affinity for 1 molecule of water which was not lost on drying over anhydrone under reduced pressure.

The two benzacridine bases fluoresced green in both alcohol and ether; the new pyridoacridine bases, green in alcohol but blue in ether, the fluorescence of 8-chloro-5-(γ-diethylaminopropylamino)-1 : 2 : 3′ : 2′-pyridoacridine in ether being a particularly vivid light blue.

Antimalarial tests were carried out on *P. gallinaceum* infections of chicks in the Biological Laboratories of Imperial Chemical Industries Ltd. Full details will be published elsewhere. The activities of the compounds prepared are shown in the Table, the activity of various doses being indicated as nil (−), doubtful (±), slight (+), or marked (++). For comparison the activities of the corresponding derivatives of 1 : 2 : 2′ : 3′-pyridoacridine and of 3 : 4 : 2′ : 3′-pyridoacridine prepared by Dobson and Kermack (*loc. cit.*) are also shown.

Ref. No.	Base.	Dose, mg./kg.	Activity.
4574	(III) R = NH·[CH$_2$]$_3$·NEt$_2$	320	Toxic
		160	−
4377	(IV) R = NH·CHMe·[CH$_2$]$_3$·NEt$_2$	120	++
		40	−
5941	(V) R = NH·[CH$_2$]$_3$·NEt$_2$	160	Toxic
		80	± (Toxic)
6443	(VI) R = NH·[CH$_2$]$_3$·NEt$_2$	160	± (Toxic)
		80	−
3476	(I) R = NH·[CH$_2$]$_3$·NEt$_2$	125	−
3652	(II) R = NH·[CH$_2$]$_3$·NEt	120	++
		80	+
		40	−
—	Mepacrine	40	++
		20	+

Of the two benzacridines and four pyridoacridines listed the most active base is that derived from 3 : 4 : 2′ : 3′-pyridoacridine. The analogous 3 : 4-benzacridine has also considerable activity, but the base derived from 3 : 4 : 3′ : 2′-pyridoacridine (in non-lethal doses) has only doubtful activity. The only 3 : 4-benzacridine base available contained the 5-diethylamino-α-methylbutylamino-side chain, but analogous results in the pyridoacridine series suggest that there would be little difference between this and the compound with the γ-diethylaminopropylamino-side chain. The benzacridine and the two pyridoacridines in which the extra ring is fused on to the 1 : 2 position of the acridine nucleus are all devoid of significant antimalarial activity. Compound No. 6443 [8-chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 3′ : 2′-pyridoacridine] was tested in the form of the hydrated crystals, m. p. 99—100°, which contained about 25% of 8-chloro-3 : 4 : 3′ : 2′-pyridoacridone; the failure of the 3 : 4 : 3′ : 2′-pyridoacridine base to be significantly active shows that the geometrical form of the heterocyclic nucleus, though evidently important, is only one factor out of several which determine the chemotherapeutic activity. All the compounds shown in the Table contain a chlorine atom in position 8 of the acridine nucleus; without this substituent even the 3 : 4 : 2′ : 3′-pyridoacridine base has only slight activity.

Experimental.

5 : 8-*Dichloro*-1 : 2-*benzacridine*.—Potassium 2 : 4-dichlorobenzoate (45·8 g.), α-naphthylamine (28·6 g.), amyl alcohol (50 c.c.), and copper bronze (0·3 g.) were refluxed at 150° for 6 hours. After cooling, the violet solid was filtered off, washed with acetone and dissolved in hot dilute ammonia, the solution filtered, and the filtrate made acid with acetic acid; 4-chloro-2-α-naphthylaminobenzoic acid was then precipitated. Yield, 48·3 g. Pale violet needles from alcohol, m. p. 232°. (Bachman and Picha, *loc. cit.*, give m. p. 236—237·5°.) This acid (24 g.) and phosphoryl chloride (100 c.c.) were refluxed at 150° for 4 hours. The excess of phosphoryl chloride was removed under reduced pressure, and the residue triturated with 2N-sodium hydroxide and ice. The solid residue was separated, dried in a desiccator, and crystallised from dry benzene. Yield, 18 g.; m. p. 192—193°. Further recrystallisation from dry benzene raised the m. p. to 201°. Bachman and Picha (*loc. cit.*) give m. p. 201—202° (Found C, 68·5; H, 2·85; N, 4·7. Calc. for $C_{17}H_9NCl_2$: C, 68·45; H, 3·0; N, 4·7%).

8-*Chloro*-5-(γ-*diethylaminopropylamino*)-1 : 2-*benzacridine*.—This was prepared from 5 : 8-dichloro-1 : 2-benzacridine (6 g.) and γ-diethylaminopropylamine (3·5 g.) in dry phenol (50 g.) at 100° for 2 hours. The base was isolated by pouring the phenol mixture into 2N-sodium hydroxide (300 c.c.), extracting the oily solid with ether, shaking the ethereal extract with 5% acetic acid, and reprecipitating with ammonia. The *base* was finally extracted with ether, the ether extract dried (K_2CO_3), and the ether removed by distillation. The residual oily solid was boiled with dry ligroin and separated as a yellow crystalline solid on cooling. It was further purified from dry ligroin, and the yellow needles melted at 113° (Found :

C, 73·8; H, 6·4; N, 10·6. $C_{24}H_{26}N_3Cl$ requires C, 73·6; H, 6·6; N, 10·7%). Bachman and Picha (*loc. cit.*) describe the dihydrochloride, m. p. 253—255°.

4-Chloro-2-β-naphthylaminobenzoic Acid.—This was prepared from potassium 2 : 4-dichlorobenzoate (45·8 g.) and β-naphthylamine (28·6 g.) in amyl alcohol (50 c.c.) with copper bronze (0·3 g.) at 150° for 6 hours. The *acid* was isolated as described for the α-acid. Yield, 45·4 g. Pale violet needles from alcohol, m. p. 272° (Found : C, 68·2; H, 4·3; N, 4·8. $C_{17}H_{12}O_2NCl$ requires C, 68·6; H, 4·0; N, 4·7%).

5 : 8-Dichloro-3 : 4-benzacridine.—This was prepared from 4-chloro-2-β-naphthylaminobenzoic acid (16 g.) and phosphoryl chloride (60 c.c.) at 150° for 4 hours. The product was isolated as described for 5 : 8-dichloro-1 : 2-benzacridine. Yield, 11·6 g. *5 : 8-Dichloro-3 : 4-benzacridine* recrystallised from dry benzene to yield pale orange-yellow needles, m. p. 175—176° (Found : C, 68·9; H, 2·9; N, 4·9%).

8-Chloro-5-(δ-diethylamino-α-methylbutylamino)-3 : 4-benzacridine.—This was prepared from 5 : 8-dichloro-3 : 4-benzacridine (5 g.) and δ-diethylamino-α-methylbutylamine (3·5 g.) in dry phenol (50 g.) at 100° for 2 hours. The base, an oil, was isolated as described above, and yielded a crystalline *picrate* which recrystallised from ethyl alcohol in canary-yellow needles, m. p. 176° (Found : C, 51·8; H, 4·1; N, 14·65. $C_{26}H_{30}N_3Cl,2C_6H_3O_7N_3$ requires C, 52·0; H, 4·1; N, 14·4%).

4-Chloro-5'-quinolylanthranilic Acid.—5-Aminoquinoline (7·4 g.) and potassium 2 : 4-dichlorobenzoate (11·4 g.) were condensed in amyl alcohol (10 c.c.) in the presence of copper bronze (0·1 g.) as described for 4-chloro-2-α-naphthylaminobenzoic acid. The product after removal of the amyl alcohol by steam distillation was filtered off, extracted with 2N-potassium hydroxide on the boiling water-bath, filtered, and the filtrate made acid with acetic acid. The precipitate after being filtered off and dried crystallised from alcohol as yellow-brown needles, m. p. 244°. Yield, 8·2 g. (Found : C, 61·4; H, 3·8; N, 9·25. $C_{16}H_{11}O_2N_3Cl,\frac{3}{4}H_2O$ requires C, 61·5; H, 4·0; N, 9·0%).

5 : 8-Dichloro-1 : 2 : 3' : 2'-pyridoacridine.—4-Chloro-5'-quinolylanthranilic acid (5 g.) was refluxed with phosphoryl chloride (30 c.c.) containing phosphorus pentachloride (0·5 g.) for 6 hours in an oil-bath at 150°. The product was worked up as described for 5 : 8-dichloro-1 : 2-benzacridine, except that during crystallisation from dry benzene a pellet of potassium hydroxide was added to prevent hydrolysis to 8-chloro-1 : 2 : 3' : 2'-pyridoacridone. *5 : 8-Dichloro-1 : 2 : 3' : 2'-pyridoacridine* formed buff-coloured needles, m. p. 244°. Yield, 3·7 g. (Found : C, 63·9; H, 2·85; Cl, 24·0. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; Cl, 23·7%).

8-Chloro-5-(γ-diethylaminopropylamino)-1 : 2 : 3' : 2'-pyridoacridine.—5 : 8-Dichloro-1 : 2 : 3' : 2'-pyridoacridine (1 g.) and γ-diethylaminopropylamine (1 g.) were condensed in dry molten phenol at 100° as described for 8-chloro-5-(γ-diethylaminopropylamino)-1 : 2-benzacridine. *8-Chloro-5-(γ-diethylaminopropylamino)-1 : 2 : 3' : 2'-pyridoacridine* forms bright yellow needles from ligroin, m. p. 98—99° (Found : C, 70·5; H, 6·35; N, 14·1; Cl, 9·15. $C_{23}H_{25}N_4Cl$ requires C, 70·3; H, 6·4; N, 14·3; Cl, 9·0%).

4-Chloro-7'-quinolylanthranilic Acid.—7-Aminoquinoline (14·8 g.) and potassium 2 : 4-dichlorobenzoate (22·8 g.) were condensed in amyl alcohol (20 c.c.) in the presence of copper bronze as described for 4-chloro-5'-quinolylanthranilic acid. The product proved very difficult to crystallise, but a brown compound, m. p. 289°, was obtained from a fairly concentrated alcoholic solution. This material (0·5 g.) was refluxed gently for 1 hour with ethanol (10 c.c.) and concentrated sulphuric acid (4 c.c.). The mixture was allowed to cool, poured on ice, left for ½ hour, and made alkaline with ammonia. The resulting precipitate crystallised from alcohol as brownish needles of *ethyl 4-chloro-7'-quinolylanthranilate*, m. p. 76—77° (Found : C, 66·6; H, 4·8; N, 8·35. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6%).

5 : 8-Dichloro-3 : 4 : 3' : 2'-pyridoacridine.—4-Chloro-7'-quinolylanthranilic acid (15 g.) was refluxed with phosphoryl chloride (90 c.c.) containing phosphorus pentachloride (1·5 g.) for 6 hours at 150° as described for 5 : 8-dichloro-1 : 2 : 3' : 2'-pyridoacridine. The product consisted of light brown needles, m. p. 209°. Repeated recrystallisations failed to alter the m. p., but the compound on analysis proved to contain 8-chloro-1 : 2 : 3' : 2'-pyridoacridone possibly as a molecular complex (Found : C, 65·2; H, 2·95; N, 9·2; Cl, 21·2. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·7. $3C_{16}H_8N_2Cl_2,C_{16}H_9ON_2Cl$ requires C, 65·2; H, 2·8; N, 9·5; Cl, 21·1%).

8-Chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 3' : 2'-pyridoacridine.—6 : 8-Dichloro-3 : 4 : 3' : 2'-pyridoacridine (1 g.) (containing some 8-chloro-3 : 4 : 3' : 2'-pyridoacridone as the analytical results showed) and γ-diethylaminopropylamine (1 g.) were condensed in dry molten phenol at 100° for 2 hours as described for 8-chloro-5-(γ-diethylaminopropylamino)-1 : 2-benzacridine. The product (0·8 g.) consisted of orange-yellow needles, m. p. 99—100°. Further recrystallisation from dry ligroin left this m. p. unchanged. The analytical figures were consistent with the presence of some pyridoacridone and water (Found C, 67·8; H, 6·0; N, 12·5; Cl, 9·55. $C_{23}H_{25}N_4Cl$ requires C, 70·3; H, 6·4; N, 14·3; Cl, 9·0. $3C_{23}H_{25}N_4Cl,C_{16}H_9ON_2Cl,3H_2O$ requires C, 67·5; H, 5·9; N, 13·0; Cl, 9·4%). Some of this material was dried over anhydrone under reduced pressure at room temperature; it was then found to have lost 4·2% by weight (loss of $3H_2O$ requires 3·6%). Some of this dried material was recrystallised from specially dried heptane yielding a *base*, m. p. 69—70°, which seemed free from pyridoacridine but still contained one molecule of water of crystallisation (Found : C, 66·7; H, 6·55; N, 14·0. $C_{23}H_{25}N_4Cl,H_2O$ requires C, 67·2; H, 6·6; N, 13·6%).

We are indebted to Imperial Chemical Industries Ltd. for facilities in connection with the above work, and thank their analytical department for the microanalyses.

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33. *Synthesis of a Zeolitic Mineral with Chabazite-like Sorptive Properties.*

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By heating synthetic and natural analcites with water and excess of barium or potassium chloride or bromide, it was found possible under certain conditions to produce new aluminosilicates as characteristic small rectangular crystals. Similar products were obtained from synthetic or natural leucites, and from gels similar to but not necessarily identical with analcite in the proportions of base : Al_2O_3 : SiO_2. In these gels the base could be BaO, CaO, K_2O, or Na_2O, provided always that the mineralising salt was present in excess. The best proportions of analcite : water : salt for the recrystallisation were studied and it was demonstrated that bromides and chlorides of potassium or barium were specific mineralisers for the reaction, which did not take place with the salts $CaCl_2$, $SrCl_2$, KNO_3, $Ba(NO_3)_2$, and KF.

The minerals produced contained large amounts of interstitially incorporated mineralising salt, but all the products were believed to be based on the same or similar aluminosilicate frameworks. This was proved by *X*-ray photographs to be the case for the minerals containing barium chloride and bromide. Analyses of the mineral containing the chloride gave approximately the composition $BaO,Al_2O_3,4SiO_2,xBaCl_2,yH_2O$, where x varied between 0·6 and 0·8 and y between 3 and 2.

The interstitially incorporated salt could be removed by high-temperature extraction with distilled water, with a minimum of alteration of the parent aluminosilicate framework in the case of the mineral containing barium chloride, with a marked tendency to produce a new species when the parent mineral contained barium bromide, and with decomposition when it contained potassium chloride. The unaltered but salt-free aluminosilicate proved to be a zeolitic molecular sieve sorbent having sorptive properties similar to those of chabazite but based upon a different crystalline structure. The sorptive behaviour is studied in the following paper.

Zeolites are believed to arise through the mineralising action of solutions on rocks under relatively stagnant and possibly rather alkaline conditions, between 100° and 350° (Lindgren, " Mineral Deposits ", McGraw-Hill Book Co., 1919, 427). These hydrous minerals are endowed with base-exchange properties, and sometimes, when dehydrated, with remarkable gas-absorbing powers and molecular-sieve characteristics. Although they occur in widespread localities they are not usually found in quantity, except in a few instances such as mordenite.

One of the best gas-absorbing zeolites is chabazite $(Ca,Na_2)Al_2Si_4O_{12},6H_2O$, with sorbing power equal to that of active charcoals, and in addition with singularly clear-cut molecular-sieve properties which enable it to effect a great variety of separations of mixtures by selective sorption (Barrer, *J. Soc. Chem. Ind.*, **1945**, **64**, 130, 131, 134). This mineral has not so far proved easy to make or there is little doubt that it would find many applications as a selective special purpose sorbent. Its behaviour has led it to be described as a Class 1 molecular sieve, using certain molecules as yardsticks in defining the types of molecule which will or will not be sorbed. Thus it cannot sorb *iso*paraffins (*e.g.*, $CHMe_3$) but sorbs *n*-paraffins (CH_2Me_2) slowly, and molecules such as ethane or methane with great rapidity (Barrer, *loc. cit.*; Barrer and Ibbitson, *Trans. Faraday Soc.*, **1944**, **40**, 195, 206). Corresponding to these typical molecules it was shown that chloroform, bromoform, *sec.*-propyl alcohol, and other molecules of similar shape and size to *iso*butane were not sorbed; methylene chloride or bromide and other molecules of similar shape and size to propane were slowly sorbed; and molecules like methanol and methyl cyanide similar in shape and size to ethane were rapidly sorbed. The molecular-sieve property arises because the dehydrated lattice of the sorbent is traversed by channels of molecular dimensions too narrow to accommodate some molecules but wide enough to contain others (Barrer, *loc. cit.*).

Many types of mixtures can be resolved by using different classes of molecular-sieve sorbent; *inter alia*, chabazite can separate *n*-paraffins quantitatively from *iso*-paraffins and aromatic hydrocarbons; methyl chloride and methylene dichloride from chloroform and carbon tetrachloride; water, methanol, and ethanol from higher alcohols, or from ketones and ethers; or simple monosubstituted methanes (CH_3Br, $CH_3{\cdot}CN$, $CH_3{\cdot}NH_2$, etc.) from similar monosubstituted ethanes, propanes, and so on (Barrer, *loc. cit.*; B.P. Appln. No. 15561/43; *ibid.*, No. 548,905; U.S.P. No. 2,306,610). One can thus see that peculiar interest attaches to syntheses of molecular-sieve sorbents.

Many attempts were made to synthesise chabazite, but although these led to the preparation of several calciferous aluminosilicates, they were not successful in their primary object. However, the present paper describes the synthesis of a new zeolitic mineral which possesses the same molecular-sieve characteristics as chabazite itself (see following paper). The new mineral does not appear to occur naturally.

Experimental.

Aluminosilicate gels or minerals were crystallised or recrystallised hydrothermally in stainless-steel autoclaves, capable of sealing the mineralising solutions at temperatures up to 400°, and thus at several hundred atm. pressure of water vapour. These autoclaves were prepared according to a small number of simple designs. The smaller had internal volumes of *ca.* 10 c.c., and the larger of *ca.* 25 c.c. Sealing was effected by soft copper washers which flowed slightly under pressure when the cap of the autoclave was tightly screwed down. Lead washers were also tried, but flowed too readily at temperatures above 220°.

Substances treated with mineralising solutions included analcite ($NaAlSi_2O_6,H_2O$), leucite ($KAlSi_2O_6$), chabazite, bentonite, a variety of aluminosilicate gels specially prepared, and base-exchange gel zeolites sold under the trade names "Doucil", "Burgess Freeze Formed Zeolite" and "Permutit". Synthetic gels were prepared by dissolving known weights of previously analysed sodium aluminate ("Alfloc") in water, and stirring it into a creamy suspension of silicic acid gel of known silica content. The mixture was then evaporated to dryness. The powdered product was in some instances base-exchanged by salts of cations such as Ca^{++}, Ba^{++}, or K^+, to produce powdered gels rich in these cations. As a rule, however, the sodium-rich gels were used as such.

Synthetic as well as natural leucite and analcite were among the crystalline minerals used. Analcite was prepared from gels of approximate compositions $Na_2O,Al_2O_3,4SiO_2,xH_2O$, by hydrothermal crystallisation with distilled water at temperatures which in different preparations ranged from 150° to 300°. The duration of heating was usually about 24 hours, and a temperature of 200—220° was then very effective. Synthetic leucite was obtained from analcite by base exchange of Na^+ using K^+ in excess, for similar times and at similar temperatures.

Preparation of a New Group of Minerals.—The first successful conversion of analcite into a member of the new group of minerals was observed when analcite powder was mixed with about its own volume of barium chloride, water was added equal in amount to the total apparent volume of solids, and the whole heated at 210° for 2 days. In subsequent experiments the salt was varied from 0·5 to 1·5 times the volume of analcite, and the water over a similar range in volumes, without finding any critical conditions. The various mixtures were heated to temperatures ranging from 180° to 270°, being given progressive treatments of from 2 to 6 days. Recrystallisation was observed in all cases, being most extensive in the temperature range 180—220°. The analcite ikositetrahedra were converted into small rectangular crystals (see fig. 1).

Similar experiments to those described above were next carried out, various minerals and gels being used in place of analcite (Table I). All the experiments were successful save those with the minerals chabazite and bentonite, and it is obvious that some latitude is possible in the composition and character of the gel. Further successful series of experiments were conducted with barium bromide in place of barium chloride as mineralising salt (Table II). Potassium chloride and bromide were also employed with success, as can be seen in the figures, the conditions being similar to those used in the experiments with the barium salts, with a recrystallising temperature of 240°.

The reaction depended specifically upon the character of both cation and anion. Thus NaCl, $SrCl_2$, and $CaCl_2$ were ineffective, and show the effect of varying the cation; KNO_3, KF, and $Ba(NO_3)_2$ were equally ineffective both with analcite and with a gel of the same composition. Base exchange only was now found, which could be complete in the case of the potassium salts, but was never more than partial with analcite and $Ba(NO_3)_2$. On raising the reaction temperature to 300° base exchange of $2Na^+$ by Ba^{++} in analcite became complete, but instead of recrystallisation a product amorphous to *X*-rays was obtained.*

As appears often to be the case in hydrothermal crystallisation of silicates (Baur, *Z. anorg. Chem.*, 1911, **72**, 119), the crystallites deposited were very small, and when once formed showed little tendency to further growth. Thus crystals derived in an earlier experiment were given a further 15 days' hydrothermal treatment with water and barium chloride, without a sensible increase in size.

The Composition and Nature of the New Species.—Analysis revealed that the halide ($BaCl_2$, $BaBr_2$, KCl, and KBr) had entered into the composition of the minerals illustrated in Figs. 2—5, almost certainly as an interstitial solid solution. The interstitial character was shown by extracting the minerals in autoclaves with distilled water at about 200°, whereupon large amounts of halide (which could not be extracted simply by refluxing with water at 100°) appeared in the mother-liquor. A number of analyses were then made on small amounts of different preparations of the mineral containing barium chloride † (Table III). In spite of small deviations the "ideal" composition of the mineral was taken to be $(Na_2O,BaO),Al_2O_3,4SiO_2,xBaCl_2,yH_2O$, where the interstitial $BaCl_2$ and H_2O contents may vary somewhat, but where x is not far from 0·66.

X-Ray powder photographs were made of the minerals containing barium chloride and bromide. The main spacings are given in Table IV, and, in view of the sorptive properties described in the next paper, some main spacings for chabazite in the same range were also determined. It is clear that the minerals containing these two barium salts are based upon the same space lattice, which is not identical with the chabazite space lattice. When the occluded barium chloride or bromide was removed from the lattice as described on p. 132, giving the products of cols. 3 and 4, the lattice spacings show some shrinkage and variability, but the same aluminosilicate framework is still recognised. The extent of shrinkage is believed to depend upon the severity and extent of the extraction process, which sometimes if too prolonged gave an "amorphous" band, and also resulted in partial recrystallisation. Even the parent mineral containing barium chloride showed spacings with minor variation (col. 1, Table IV) which may be associated with variations in barium chloride content (cf. Table III).

* Analysis of this material gave SiO_2, 43·92; Al_2O_3, 20·12; BaO, 27·42; H_2O, 6·84%; Na_2O, not determined. The molar proportions were respectively 0·732, 0·197, 0·179, and 0·380, *i.e.*, the composition is $0{\cdot}98BaO,1{\cdot}07Al_2O_3,4{\cdot}00SiO_2,2{\cdot}08H_2O$, the constituents still being in analcite proportions.

† The amount of mineral used per analysis ranged from 0·5 to 1·0 g.

TABLE I.

Typical preparations of the mineral obtained with barium chloride as mineraliser.

Aluminosilicate component.	Treatment.	Temp.	Yield of mineral.
Naturally occurring analcite	Five progressive treatments with fresh charges of H_2O and $BaCl_2$, each of 12 hours' duration	200°	Excellent
Naturally occurring analcite	Four progressive treatments as above, each of 1 day	233	Good to moderate
Synthetic analcite	Six progressive treatments as above, each of 1 day	210	Excellent
Natural leucite	Four days' continuous heating with one charge of H_2O and $BaCl_2$	218	Appreciable
Synthetic leucite	Two days' continuous heating with one charge of H_2O and $BaCl_2$	208	Moderate
Synthetic leucite	Two days' continuous heating with one charge of H_2O and $BaCl_2$	218	Fine growth of crystals of new mineral
" Burgess Freeze Formed " gel zeolite	Five days' continuous heating with one charge of H_2O and $BaCl_2$	208	Good
Ca-base-exchanged " Doucil " gel zeolite	Six days' continuous heating with one charge of H_2O and $BaCl_2$	180	Crystallisation not noted
Gel as above	Five days' continuous heating with one charge of H_2O and $BaCl_2$	208	Excellent
Potassium aluminosilicate gel, $K_2O,Al_2O_3,4SiO_2,nH_2O$	Six days' continuous heating with one charge of H_2O and $BaCl_2$	180	Excellent
Barium aluminosilicate gel, $BaO,Al_2O_3,4SiO_2,nH_2O$	Three days' continuous heating with one charge of H_2O and $BaCl_2$	235	Good
Gel as above	Treatment as above	270	Moderate
Gel as above	One day's heating at 210° and two days' heating at 197°, with one charge of H_2O and $BaCl_2$	—	Good
Chabazite	Five days' heating with one charge of H_2O and $BaCl_2$	208	Slight evidence of crystal growth
Chabazite	Three days' heating with one charge of H_2O and $BaCl_2$	218	No evidence of crystal growth
Bentonite	Seven days' heating with one charge of H_2O and $BaCl_2$	200	No evidence of alteration in bentonite

TABLE II.

Typical preparations of the mineral obtained with barium bromide as mineraliser.

Aluminosilicate component.	Treatment.	Temp.	Yield of mineral.
Synthetic analcite	Two progressive treatments with fresh charges of H_2O and $BaBr_2$ of two days and 30 hours respectively	205°	Excellent
Barium aluminosilicate gel, $BaO,Al_2O_3,4SiO_2,nH_2O$	Treatment as above	205	Negligible yield
" Burgess Freeze Formed " gel zeolite	Two days' treatment with H_2O and $BaBr_2$	205	Small, as very tiny crystals
Gel as above	Treatment as above	220	Improved yield
" Permutit " gel zeolite	Treatment as above	205	Small, as very tiny crystals
Gel as above	Treatment as above	220	Improved yield

TABLE III.

Typical analytical results.

	% by weight in analysis no.:				Molar proportions in analysis no.:			
Component.	1.	2.	3.	4.	1.	2.	3.	4.
SiO_2	36·91	36·8	36·8	33·85	4·00	4·00	4·00	4·00
Al_2O_3	16·26	16·16	not detd.	15·29	1·04	1·03	—	1·06
BaO	20·98	18·55	19·72	20·03	0·89	0·79	0·84	0·93
Na_2O	not detd.	not detd.	none	0·28	—	—	—	0·03
$BaCl_2$	22·1	19·85	19·85	23·88	0·69	0·62	0·62	0·81
H_2O	not detd.	8·5	not detd.	6·06	—	3·08	—	2·40
Fe_2O_3	0·2	trace	trace	not detd.	—	—	—	—

TABLE IV.

Some main X*-ray diffraction spacings* (A.) *in the new minerals and allied products.*

Mineral containing $BaCl_2$.			Mineral † containing $BaBr_2$.	Mineral originally containing $BaCl_2$ after extraction of $BaCl_2$.			Mineral § originally containing $BaBr_2$ after extraction of $BaBr_2$ and some re-crystallisation.	Chabazite ‖ spacings (lines over similar range only).
(1) *	(2) *	(3) *		(1) ‡	(2) ‡	(3) ‡		
—	—	13·10 (s)	13·57 (v.s.)	—	—	—	12·67(w)	18·7 (m.s.)
—	—	9·40 (m)	—	—	—	—	[9·52 (m)]	—
—	—	5·96 (w)	—	6·16 (v.v.w.)	—	—	[7·65 (m)]	6·74 (w)
—	4·90 (v.w.)	5·01 (w)	4·98 (m)	—	—	—	[6·31 (m)]	5·52 (m.s.)
—	4·38 (m)	4·43 (m)	4·44 (s)	—	—	—	4·90 (w)	4·97 (m.s.)
—	4·15 (v.w.)	4·16 (w)	4·17 (m)	—	—	—	[4·00 (m)]	4·30 (v.s.)
—	3·79 (m.w.)	3·81 (m)	3·82 (m)	—	—	—	3·77 (w)	—
3·15 (w)	3·19 (w)	3·20 (s)	3·21 (m)	—	—	3·15 (w)	3·26 (w)	3·86 (m)
2·90 (v.w.)	3·02 (m)	3·03 (v.s.)	3·04 (s to v.s.)	2·99 (m)	2·96 (m)	2·90 (v.w.)	[3·12 (m)]	3·57 (m.s.)
2·72 (v.w.)	2·80 (m)	2·82 (m)	2·82 (s)	2·79 (m)	2·75 (w)	2·72 (v.w.)	[2·66 (m)]	3·45 (m.w.)
2·60 (v.w.)	2·64 (v.v.w.)	2·64 (w)	—	—	2·57 (m)	2·60 (w)	—	3·19 (w)
—	2·51 (w)	2·45 (v.w.)	2·54 (w)	—	—	—	—	2·91 (v.s.)
—	2·35 (v.w.)	—	—	—	—	—	—	2·67 (v.w.)
—	2·30 (w)	2·30 (w)	2·29 (w)	2·25 (v.w.)	—	—	2·33 (v.w.)	2·60 (m)
—	—	1·90 (v.v.w.)	—	—	—	—	2·07 (v.w.)	2·55 (m)
—	—	1·79 (v.v.w.)	—	—	—	—	—	2·33 (w)
—	—	1·76 (v.v.w.)	—	—	—	—	—	2·29 (w)
								2·09 (m)
								1·92 (v.v.w.)
								1·86 (w)
								1·80 (m)
								1·73 (w)

* (1) Prepared from synthetic analcite at 210°.
* (2) Prepared from natural analcite at 210°.
* (3) Prepared from natural analcite at 208°.
† Prepared from synthetic analcite at 205°.
‡ (1) Product of col. 1, preparation (2).
‡ (2) Product of col. 1, preparation (1).
‡ (3) Prepared from synthetic analcite and $BaCl_2$.aq. at 235° and subsequently extracted.
§ Prepared from synthetic analcite and $BaBr_2$ at 204°. Lines in square brackets are due to recrystallisation during extraction, giving a new type of crystal.
‖ A natural calcium-rich sample.

FIG. 1.

Crystals of ikositetrahedral synthetic analcite amid smaller crystals of new mineral prepared by partial recrystallisation of the parent analcite, using $BaCl_2$. *Magnification* 200.

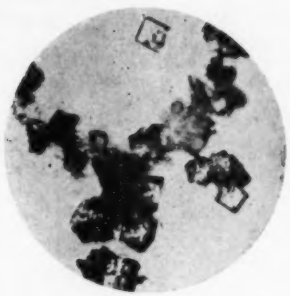

FIG. 2.

Rectangular crystals of the new mineral, $BaO,Al_2O_3,4SiO_2,0{\cdot}66BaCl_2,\ 2{-}3H_2O$, *produced by recrystallising analcite, using* $BaCl_2$. *Magnification* 400.

FIG. 3.

Crystals of similar species grown from synthetic analcite using $BaBr_2$ *in place of* $BaCl_2$. *Magnification* 400.

FIG. 4.

Crystals of similar species grown from synthetic leucite using KCl. *Magnification* 200.

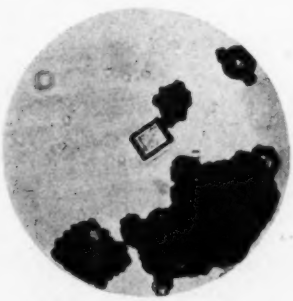

FIG. 5.

Occasional crystals of similar species to Figs. 2, 3, *and* 4, *grown from synthetic leucite using* KBr. *Magnification* 200.

FIG. 6.

The crystals of rectangular contour are similar to those in Fig. 2, *but with the* $BaCl_2$ *removed by hydrothermal extraction. The typical elongated crystal is also produced by a partial recrystallisation of the barium mineral of Fig.* 2 *during hydrothermal extraction of the chloride. Magnification* 400.

[*To face p.* 130.

Although the spacings in col. 4 show a slight similarity between chabazite and the new mineral, this similarity is at best only qualitative. There is some resemblance in the crystalline forms : chabazite occurs characteristically as rhombs with an angle of nearly 90°, whereas Figs. 2—5 show the new mineral to consist of nearly rectangular blocks. These crystals were very nearly isotropic, or at most very feebly birefringent.

Limiting Conditions for Recrystallising Analcite.—Systematic variation in the composition of the reaction mixture was undertaken to define more closely the critical conditions for obtaining the new minerals from analcite (Table V). The volume within the autoclaves was about 25 c.c., so that as the

TABLE V.

Yield in relation to composition of reaction mixture and other factors.

Mineral containing $BaCl_2$.

	Composition.	Conditions.	Yield.
(1)	Analcite 5·23 g., $BaCl_2$ 7·78 g., H_2O 5 c.c.	44 Hrs. at 197°	Excellent. Very small amount unaltered analcite
(2)	Analcite 5·23 g., $BaCl_2$ 7·78 g., H_2O 10 c.c.	As above	Good. Crystals larger than in (1), but amount of unaltered analcite larger
(3)	Analcite 5·23 g., $BaCl_2$ 7·78 g., H_2O 15 c.c.	As above	Moderate yield. Unaltered analcite increasing in amount
(4)	Analcite 3·67 g., $BaCl_2$ 5·50 g., H_2O 18 c.c.	Three days at 173°	No observable yield of new mineral
(5)	Analcite 3·36 g., $BaCl_2$ 5·00 g., H_2O 18 c.c.	Two days at 197°	As in (4)
(6)	Analcite 3·36 g., $BaCl_2$ 5·00 g., H_2O 13·2 c.c.	As in (5)	Rare crystals of new mineral. Mainly analcite
(7)	Analcite 3·36 g., $BaCl_2$ 5·55 g., H_2O 13·2 c.c.	As in (5)	As in (6)

Mineral containing $BaBr_2$.

	Composition.	Conditions.	Yield.
(1)	Analcite 3·36 g., $BaBr_2$ 5·00 g., H_2O 15 c.c.	Two days at 194°	Only analcite present
(2)	Analcite 3·36 g., $BaBr_2$ 8·00 g., H_2O 15 c.c.	42 Hrs. at 194°	Small yield new mineral. Some crystals projecting from analcite matrices
(3)	Analcite 3·36 g., $BaBr_2$ 10·0 g., H_2O 15 c.c.	Two days at 194°	Some quite well-formed crystals, but much analcite
(4)	Analcite 3·36 g., $BaBr_2$ 12·00 g., H_2O 15 c.c.	Two days at 194°	Fair yield, but still considerable analcite
(5)	Analcite 3·36 g., $BaBr_2$ 14·00 g., H_2O 15 c.c.	As in (4)	As in (4)
(6)	Analcite 3·36 g., $BaBr_2$ 10·00 g., H_2O 8 c.c.	As in (4)	Increased yield of new mineral
(7)	Analcite 3·36 g., $BaBr_2$ 10·00 g., H_2O 6 c.c.	As in (4)	As in (6)
(8)	Analcite 3·36 g., $BaBr_2$ 10·00 g., H_2O 8 c.c.	Two days at 204°	Extensive recrystallisation, but still some analcite
(9)	Analcite 3·36 g., $BaBr_2$ 10·00 g., H_2O 8 c.c.	Two days at 209°	As in (8)
(10)	Analcite 3·36 g., $BaBr_2$ 10·00 g., H_2O 15 c.c.	Three days at 225°	Excellent yield. Small amount of analcite only

TABLE V—*continued.*

Mineral containing KCl.

Composition.		Conditions.	Yield.
(1) Analcite	6·07 g.	44 hrs. at 235°	Rare crystals of new mineral
KCl	11·52 g.		
H_2O	7 c.c.		
(2) Analcite	6·07 g.	As above	As above
KCl	9·98 g.		
H_2O	7 c.c.		
(3) Analcite	6·07 g.	As above	Increased yield of new mineral
KCl	7·98 g.		
H_2O	7 c.c.		
(4) Analcite	6·07 g.	As above	Yield as in (3)
KCl	5·00 g.		
H_2O	7 c.c.		
(5) Analcite	6·07 g.	Two days at 235°	Rare crystals of new mineral
KCl	4·00 g.		
H_2O	7 c.c.		

temperature was always well below the critical temperature of water, liquid water was always present to act as mineraliser. It appears that formation of the minerals containing barium chloride or bromide was favoured by low water : barium salt ratio for a fixed amount of analcite (Table V), while good yields were observed in the temperature range 180—220° (Tables II and V). The influence of temperature upon the yield in the reaction between analcite and aqueous barium bromide is well shown in Table V. The reaction between analcite and aqueous potassium chloride was less complete and the optimum salt : water ratio is similar to this ratio for synthesising the barium chloride-containing mineral.

Removal of Halide from the New Minerals.—The ease with which $BaCl_2$, $BaBr_2$, and KCl could be extracted from the minerals suggested that the halide was in interstitial solid solution within the aluminosilicate framework, which was the same, at least for the minerals containing barium halides (Table IV). In further test of this the barium chloride-rich minerals were progressively extracted by heating with distilled water in the autoclaves. The first mother-liquors gave very heavy precipitates with silver nitrate, but as the extraction continued the quantity of halide diminished until it was negligible. Several specimens of the extracted mineral were examined by *X*-ray diffraction, and revealed a slightly contracted form of the parent structure (Table IV, col. 3). The original small rectangular crystals were, however, somewhat pitted, and occasional crystals of another shape were also observed (Fig. 6). The yield of extracted mineral may then have been about 70% of the unextracted mineral. The conditions of extraction are recorded in Table VI.

TABLE VI.

Extraction of barium chloride from mineral containing it.

No. of extractions for removing salt	Volume ratio of water to mineral	Temp. and duration of each extraction.
10	15 : 1	24 Hrs. at 210°
10	15 : 1	As above
10	6 : 1	2 Days in range 200—270°
6	15 : 1	2 Days at 270°
7	15 : 1	36 Hrs. at 208°

A similar extraction of the barium bromide-rich mineral resulted in a much greater proportion of recrystallisation to crystals of the form shown in Fig. 6, and the yield of barium bromide-free parent mineral was correspondingly decreased. Spacings attributed to the recrystallisation product are indicated in Table IV, col. 4, and are enclosed in square brackets, the corresponding *X*-ray diffraction rings being spotty owing to the larger size of the crystallites, instead of being uniformly dark as for the original and the extracted parent mineral. It was thought that these new crystals might have been harmotome, but a comparison with *X*-ray diffraction spacings derived from a photograph of natural harmotome showed no particular correspondence. The mineral containing potassium chloride was also extracted four times by distilled water at 235°. Extraction proceeded rather more slowly than did the removal of barium chloride and bromide, and the tendency of the aluminosilicate to disintegrate led to the abandonment of this experiment.

The minerals thus freed of barium chloride and bromide were hydrated and zeolitic in character, so that when outgassed they copiously sorbed certain gases and vapours and showed the molecular-sieve characteristics described in the following paper.

I am indebted to Mr. G. Bartindale and Dr. M. Davies for *X*-ray photographs of some of the products, and to Mr. G. Styan and Dr. D. Ibbitson for some analyses. I am also glad to acknowledge facilities for photomicrographic work made available at the Royal Institution by Professor E. K. Rideal, F.R.S.

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34. *Sorptive and Molecular-sieve Properties of a New Zeolitic Mineral.*

By R. M. Barrer and D. W. Riley.

The synthetic zeolitic mineral described in the preceding paper has been used in an investigation of sorption phenomena involving among other sorbates the rare gases (He, Ne, A, and Kr), the permanent gases (O_2 and N_2), ammonia, and hydrocarbons (CH_4, C_2H_6, C_3H_8, n-C_4H_{10}).

The sorbent behaved as a molecular sieve in the same manner as chabazite. Thus it did not occlude *iso*paraffins (C_4H_{10}, C_5H_{12}, C_6H_{14}), aromatic hydrocarbons (C_6H_6), or molecules such as $CHCl_3$ and CCl_4; it sorbed the n-paraffins propane and butane and such molecules as CH_2Cl_2 slowly, and methane, ethane, and molecules of smaller cross section very rapidly. By means of this selectivity quantitative separations were effected of n- from *iso*-paraffins and aromatic hydrocarbons, the behaviour again recalling that of chabazite.

Isotherms and isobars were obtained, and sorption heats derived for many sorbates. These heats decreased in a characteristic manner as the amount of gas sorbed increased, and owing to the interstitial position of the sorbed molecule were frequently considerable, particularly for n-paraffins.

Propane and n-butane diffused slowly into the dehydrated crystal lattice by a process of activated diffusion ($D = D_0\, e^{-E/RT}$), and the rate constant for the sorption as expressed by the "parabolic" diffusion law decreased with the fraction θ of saturation of the mineral at first linearly, $D = D_1(1 - \theta)$, and then, after a relatively sharply defined value of θ, much more slowly.

Comparison isotherms using chabazite showed that the sorptive power of the new mineral was of the same order as that of chabazite. Thus, synthetic crystalline zeolites can be made whose performance as sorbents is comparable with that of the best natural zeolites. Both chabazite and the synthetic zeolite show a greater selectivity in sorbing certain of the rare gases than does charcoal, and the data suggest that separations of helium and neon would be possible at temperatures higher than those needed when using charcoal, and so more conveniently accessible on a large scale.

In the preceding paper the preparation of a new mineral was described, from analcite, leucite, and gels. This mineral normally contained salt such as barium chloride in interstitial solid solution. From it, by extraction of barium chloride, the salt-free aluminosilicate was obtained which was found to be an excellent zeolitic sorbent. The present paper gives an account of the observed sorptive properties.

The molecular-sieve properties of various gas-absorbing zeolites fall into at least three classes, each of which can effect a variety of separations of molecular mixtures (Barrer, *J. Soc. Chem. Ind.*, 1945, **64**, 130). The molecules of some components may be too large to enter the interstices of the molecular sieve, while those of others are small enough to do so freely. It was accordingly of importance to determine the molecular-sieve properties of the synthetic zeolite, and to compare it with other zeolites. This comparison was made, not only as regards selectivity, but also as regards isotherms, and energetics and kinetics of sorption, in which the new mineral showed unusual behaviour.

The technical possibilities of sorbents such as charcoal, silica gel, ferric oxide, activated alumina, and the like have been well explored. These cheap materials have a permanent place as general purpose sorbents. Nevertheless, there may be a real but unexplored place for special purpose sorbents capable of quantitative molecular-sieve actions, such as the one now to be described.

Experimental.

Substances used as sorbates included those mentioned in the summary. The four noble gases were obtained from the British Oxygen Co., helium and neon being spectrally pure, while the krypton contained 4% of xenon. Impure argon was purified as follows: it was passed over Cu–CuO mixture at 300°, to remove hydrogen and some oxygen, and through soda-lime to absorb carbon dioxide. It was then dried over phosphoric oxide, and passed over red-hot magnesium to remove nitrogen and residual oxygen. The whole process of purification was repeated once. The hydrocarbons CH_4, C_2H_6, C_3H_8, and n-C_4H_{10} were prepared by decomposing with water the Grignard compounds formed from the redistilled alkyl bromides, with subsequent drying and fractionation of the hydrocarbons. High-boiling propyl and amyl ethers were used as solvents for forming the Grignard compounds in order to simplify the separation of the hydrocarbon from the ether. In the case of methane, however, diethyl ether was suitable. Pure *iso*butane, *iso*pentane, and *iso*octane were supplied in small quantity by the Shell Marketing and Refining Co.

Oxygen gas was obtained by heating outgassed A.R. potassium permanganate in a vacuum. Nitrogen from a cylinder was passed over Cu–CuO mixture at about 300° (to remove oxygen and hydrogen), and over phosphoric oxide to remove water. Ammonia was liberated by the action of concentrated sodium hydroxide solution upon A.R. ammonium chloride in an evacuated vessel. The ammonia was dried in transit through a tube of freshly ignited quick-lime. Other potential sorbates included pure carbon tetrachloride, chloroform, and methylene chloride.

Sorption equilibria were measured by using the static method, and the apparatus was similar to one already described (Barrer and Ibbitson, *Trans. Faraday Soc.*, 1944, **40**, 195, 206).

Four different samples of the barium chloride-free aluminosilicate mineral were prepared as described in the preceding paper. These were outgassed before use at 300—360° for periods lasting up to 24 hours, a mercury diffusion pump backed by a " Hyvac " pump being used. The mineral was found to retain its sorptive power indefinitely at these temperatures, so it is a robust three-dimensional network lattice of stability to be compared with that shown by mordenite, gmelinite, or chabazite.

Low temperatures were attained by using liquid nitrogen (— 195°), liquid air (— 186°), dry ice (— 78°), and ice. Temperatures intermediate between these fixed points were obtained by a device already described (Barrer, *Proc. Roy. Soc.*, 1937, **161**, *A*, 497, Fig. 1). Vapour-pressure thermometers were employed to register these low temperatures as follows: oxygen, from — 183° to — 210°; ethylene, from — 104° to — 150°; carbon dioxide, from — 78° to — 110°; ammonia, from — 34° to — 77°; sulphur dioxide, from — 10° to — 53°. The thermometers were sensitive and quick-acting and their use permitted a satisfactory manual control of temperature.

For higher temperatures electric furnaces were used, made by winding nichrome wire on asbestos-covered glass tubes. These were placed coaxially in metal cylinders of greater diameter, and the annular space filled with kieselguhr. Temperatures of from 60° to 400° were readily obtained with suitable series resistances, and temperatures in this range were registered with mercury-in-glass thermometers calibrated against standard thermometers.

Molecular-sieve Characteristics.—The class of molecular sieve was determined, as in the case of chabazite, gmelinite, mordenite, and the like (Barrer and Ibbitson, *loc. cit.*; Barrer, *Trans. Faraday Soc.*, 1944, **40**, 555) by using certain molecules as yardsticks to determine the dimensions of the interstitial channels permeating the crystal lattice of the dehydrated zeolite and distributed along which the sorbed molecules are found.

The mineral was exposed after thorough outgassing and at various temperatures to these typical molecules, and it was established that: (*a*) *iso*Butane and benzene were not occluded, and it may be presumed that these molecules are of too great a cross-section to enter the lattice. (*b*) *n*-Butane and propane were slowly sorbed at room temperature or above, by a process of activated diffusion (p. 140). (*c*) Methane and ethane and all smaller molecules were sorbed very rapidly at all temperatures.

Comparison with the established behaviour of chabazite and gmelinite shows that the behaviour of the new mineral is the same as noted there (Barrer, 1945, *loc. cit.*), and that these are the characteristics of a Class I molecular sieve.* As required for Class I molecular sieve sorbents it was then further shown by bathing the mineral at higher temperatures (about 160°) in vapours of *iso*pentane, *iso*octane, chloroform, and carbon tetrachloride that none of these sorbates was occluded by the new mineral; but that methylene dichloride was slowly taken up by the zeolite.

After the above qualitative experiments, the separation of mixtures was attempted, the molecular-sieve property being used. The zeolite was brought into contact with binary mixtures of known composition, of which one constituent was first shown not to be occluded, and the other to be totally sorbed, under the conditions of the experiment. The fall in pressure of the mixture as sorption proceeded was then measured, and when equilibrium was established it was found that the final pressure was quantitatively equal to that of the non-sorbed components, and the fall in pressure to the amount of occlusible component. Especially in separations at room temperature, van der Waals adsorption of the non-sorbed component upon *external* crystallite surfaces of the powder was sometimes appreciable (distinguished by its small amount and nearly instantaneous occurrence; see Fig. 7). In separations where this surface adsorption was measurable, the sorbent was first bathed in the vapour of the non-sorbed component, and the equilibrium pressure p_1 read. A known pressure of a sorbable component was then added by means of a Toepler pump, giving a pressure $(p_1 + p_2)$, and the pressure fall followed as before. The pressure then fell in all cases until the pressure p_1 was again recorded. As an illustration, an experiment on the separation of *n*-butane from benzene may be described. The sorbent bathed in benzene vapour at 160° came to equilibrium when the benzene pressure p_1 was 2·66 cm. *n*-Butane was then introduced, the momentary pressure being 7·92 cm. The pressure fell slowly, however, and in a day had reached a final value of 2·66 cm. again, thereafter remaining unaltered.

The typical separations carried out were: *n*-C_4H_{10} from *iso*-C_4H_{10} at 160°, *n*-C_4H_{10} from *iso*-C_5H_{12} at 160°, *n*-C_4H_{10} from C_6H_6 at 160°, C_2H_6 from *iso*-C_4H_{10} at 160°, C_2H_6 from *iso*-C_4H_{10} at room temperature, NH_3 from *iso*-C_4H_{10} at 160°. Parallel separations can also be carried out by using chabazite (Barrer, 1945, *loc. cit.*), from which the new zeolite does not so far appear to differ in any way in its molecular sieve action.

Isotherms and Isobars.—Isotherms obtained at various temperatures and for a number of gases are shown in Figs. 1, 2, and 3. The isotherms for oxygen, nitrogen, and argon determined on sample 1 of the mineral (Fig. 1) show that little selectivity in sorption may be expected as between these gases at — 78°. There are differences, for example in the sorption of nitrogen, between the three specimens of the new zeolite used which reflect variations in the purity of the preparations,† the best of which probably was not more than 70—80% pure. Comparison isotherms of nitrogen in chabazite are also shown in Fig. 1(*d*).

Methane and ethane were sorbed at room temperatures with great rapidity; propane and butane more slowly. Isotherms for propane are shown in two sorbent samples containing the new mineral, one being clearly in higher yield than the other. Sorption of propane by chabazite (Barrer and Ibbitson, *loc. cit.*), gmelinite (Barrer, 1944, *loc. cit.*), and the synthetic zeolite, at similar temperatures of 235°, 225°, and 220°, respectively, is compared in Fig. 2(*e*). It is seen that at low pressures the synthetic

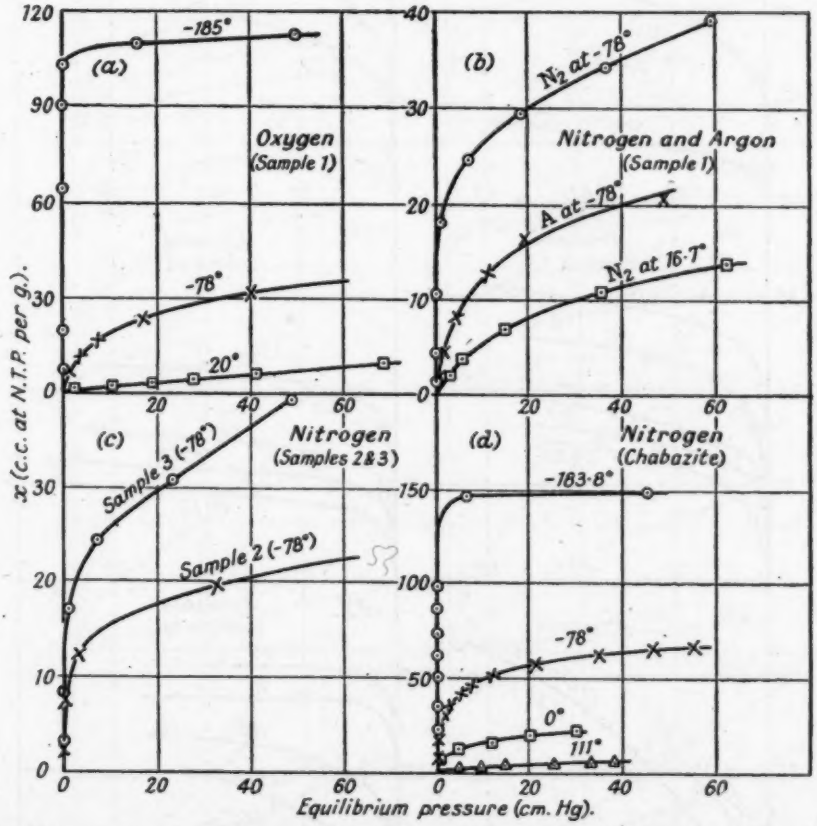
* A Class I sieve does not occlude aromatic hydrocarbons and *iso*paraffins under any conditions; it occludes *n*-paraffins slowly at room temperatures and above; and sorbs methane, ethane, and small molecules rapidly at all temperatures where sorption is appreciable.

† As shown in the preceding paper, there is some tendency to decomposition and recrystallisation during extraction of barium chloride from interstitial solid solution in the framework of the zeolite.

mineral is the most vigorous sorbent, the performance of which is striking since, as pointed out above, the synthetic product was not 100% pure. The isotherms for ammonia [Fig. 2(*f*)] illustrate the great affinity which polar gases may show for this zeolite, since even at 300° there is substantial occlusion. At room temperatures the mineral became heated following the admission of a dose of ammonia. The energetic sorption of water was also demonstrated by adding the dehydrated mineral to a little water, which became hot. This behaviour was also observed with mordenite, harmotome, and especially with chabazite.

Like oxygen and nitrogen, all the rare gases were sorbed very rapidly, freely permeating the dehydrated crystal lattice. Hence, selectivity in sorbing these smaller atoms both in chabazite and in the synthetic zeolite does not depend upon those molecular-sieve effects which permit separation for example of *n*- and *iso*-paraffins by the same zeolites, but instead depends solely upon differences in van der Waals and polarisation forces exerted on the sorbate within the lattice. Helium was sorbed only

FIG. 1.



Sorption isothermals for oxygen, nitrogen, and argon on various samples of the new mineral, and for nitrogen on natural chabazite. Note that different scales have been used for the ordinates in the several sections of the diagram.

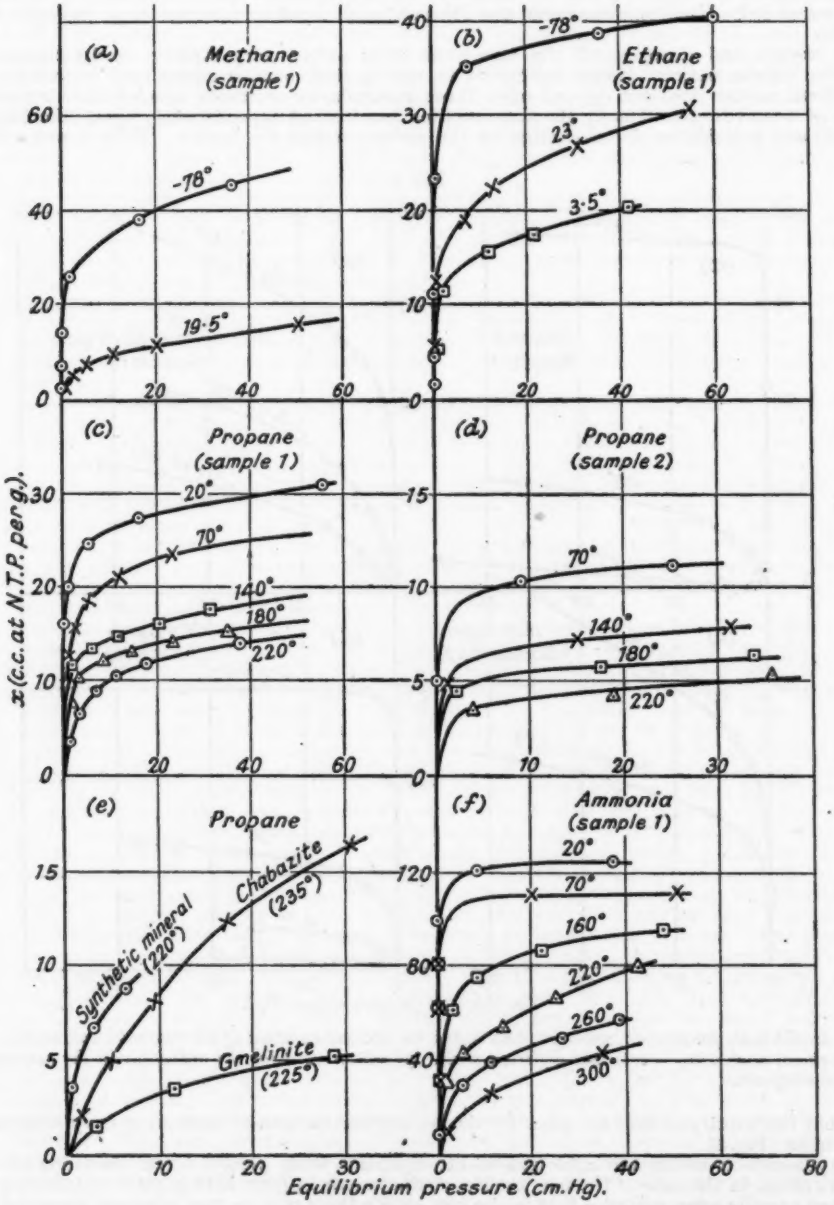
weakly, but the affinity of the rare gases for the zeolites can be seen to increase sharply with increasing atomic weight (Fig. 3).

The hydrocarbon–zeolite and noble gas–zeolite equilibria when plotted as curves of log x/p against log x were often, in the case of the new zeolite, characteristic in form with a point of inflexion. These curves then provide some evidence that in the new zeolite there may be two principal groups of sorption site available. Further evidence of this arises from the energetics and kinetics of sorption (p. 140, and Fig. 8).

These curves are useful also for estimating saturation values in some instances, saturation corresponding to a vertical log x/p–log x curve (Barrer, *Proc. Roy. Soc.*, 1938, **167**, *A*, 392, 406). Apparent saturation values may in some instances be estimated from the flattening of isobars at low temperatures (Fig. 4); or directly from isotherm data, especially when these data approximate to the Langmuir isotherm. In the latter event the slope of the graph of p/x against p gives the saturation value. These methods of deriving saturation values are in order denoted by the numbers 1, 2, and 3 given in parenthesis in Table I. For a gas like neon, where sorption is measured well above the liquefying point, and so a long way from saturation of the sorbent, method 3 can give only a lower limit, for there

is partial occupation merely of sites of greatest sorption potential, those of lesser potential being virtually unpopulated. The saturation value from the slope of the p/x–p curve must therefore refer only to an

FIG. 2.



(a) (b) (c) (f) *Isothermals on sample 1 of the new minerals.*

(c) (d) *Comparative isothermals of propane on two different samples of the new mineral.*

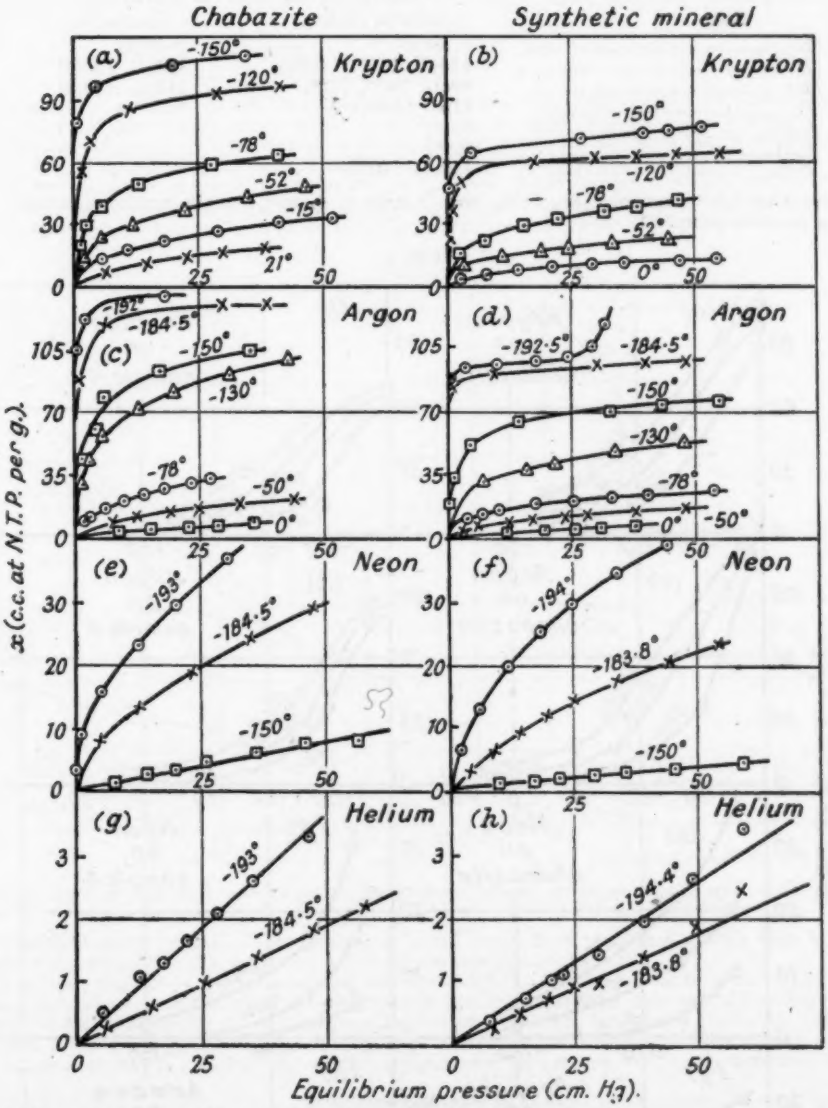
(e) *Comparative isothermals for propane on the new mineral, on natural chabazite, and on gmelinite.*

Note that different scales have been employed in the several sections of the diagram.

arbitrary range of the sites of greatest potential. The figures are unavoidably not very accurate, but the three methods lead to fairly consistent results. The saturation value given for argon in chabazite is rather lower than one already given (*idem, ibid.*; *Ann. Reports*, 1944, **41**, 31—46), but this value depends on the thoroughness of outgassing (Barrer and Ibbitson, *loc. cit.*; Lamb and Woodhouse, *J. Amer. Chem.*

Soc., 1936, **58**, 2637). Both the zeolites of Table I were outgassed under the same conditions as, but milder than, those for the sample of chabazite used previously. Referred to unit mass, the new zeolite shows saturation values about 65—75% of the corresponding figures for chabazite. The greater values for chabazite are partly due, however, to the greater density of the synthetic mineral, which contains the heavy element barium, and partly due to the lesser purity of the samples of the synthetic product.

FIG. 3.



Sorption isothermals for the noble gases on natural chabazite and on the new mineral. To avoid confusion in the cases of argon and krypton several isotherms determined at temperatures between — 50° and room temperature have been omitted from the diagrams. For the same reason many experimental points at the low-pressure ends of the isotherms have had to be omitted. Note that different scales have been employed for the ordinates for the different gases.

Referred to unit *volume* of the *pure* minerals, there may be little difference in the saturation capacity, and hence in the interstitial sorption volumes within a c.c. of each zeolite.

The two zeolites show a greater selectivity than charcoal in sorbing some of the noble gases. At — 194·7°, per g. of sorbent at an equilibrium pressure of 10 cm., sample 4 of the synthetic zeolite sorbed 17·5 c.c. at N.T.P. of neon and 0·5 c.c. of helium, giving a separation factor of 35-fold. In chabazite this factor was 27-fold; while on an active charcoal under the same conditions it was only 5-fold (Fastovskii and Girskaya, *J. Chem. Ind. U.S.S.R.*, 1937, **14**, 358). It therefore seems likely that these zeolites could

act more effectively than charcoal in separating neon and helium at temperatures readily available on a large scale (— 194° to — 210°).

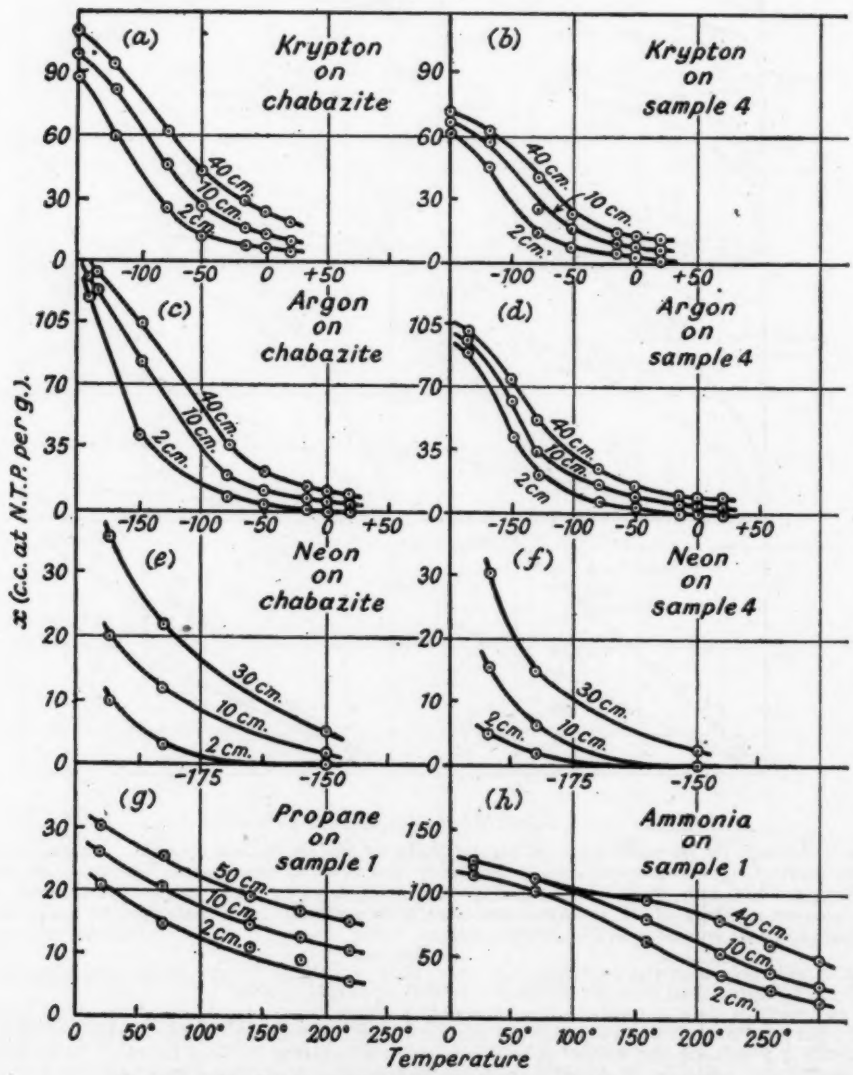
TABLE I.

*Some apparent saturation values in chabazite and in the synthetic zeolite.**

Gas.	Saturation value (c.c. at N.T.P./g.). Synthetic zeolite.	Chabazite.
Ne	>53(3)	>50(3)
A	115(2), 106(1), 105(3)	141(1), 135(3)
Kr	80(1), 78(2), 73(3)	112(1), 105(3)
O_2	115(3), 120(1)	—
C_2H_6	90(1)	—
C_3H_8	70(1)	—
NH_3	140(1), 140(2)	—

* The saturation values for C_2H_6, C_3H_8, and O_2 refer to sample 1 of the synthetic zeolite; those for the noble gases to sample 4.

FIG. 4.



Some sorption isobars on natural chabazite and on the new mineral.

Energetics of Sorption.—From the variation of the sorption equilibrium with temperature the heats of occlusion were determined. This heat can be obtained by plotting log p against $1/T$ for a given charge of gas, x, p being the corresponding equilibrium pressure. Then

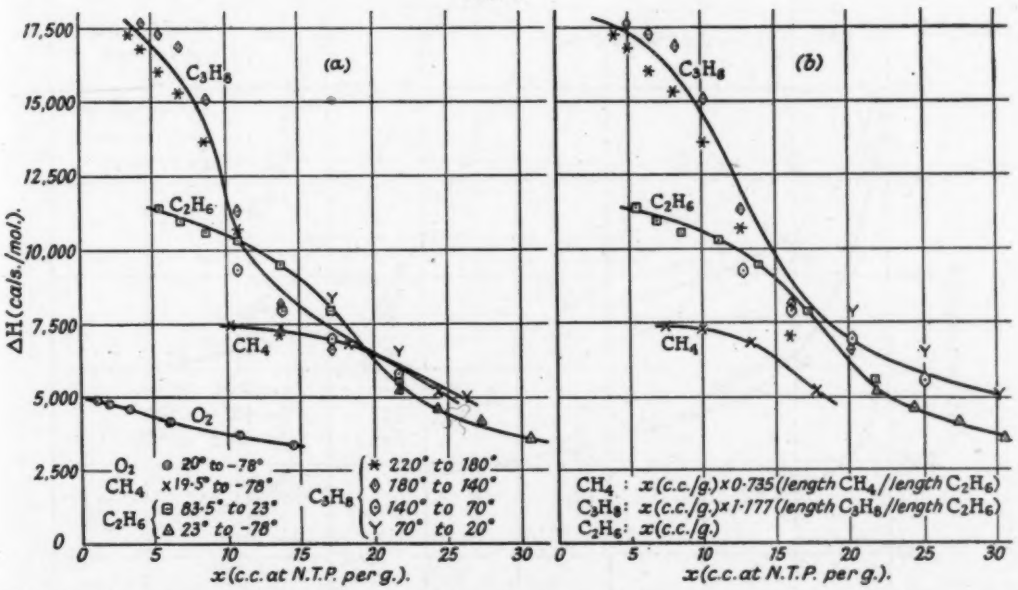
$$2{\cdot}303R\frac{\partial \log_{10} p}{\partial (1/T)} = \Delta H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Alternatively, on integration between two temperatures T_1 and T_2 the Clapeyron equation gives

$$2{\cdot}303R\left(\log_{10}\frac{p_1}{p_2}\right)\frac{T_2T_1}{T_1-T_2} = \Delta H \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

ΔH was determined by equation (1) for some of the noble gases on chabazite, and from equation (2) for oxygen and several hydrocarbons and noble gases on the synthetic mineral. By measuring ΔH at a series of different values of x, the variation in the heat of sorption as x increases can be obtained. These data are presented in Fig. 5(*a*) for O_2, CH_4, C_2H_6, and C_3H_8 in sample 1 of the new mineral, and in Figs. 6(*a*) and (*b*) for the noble gases in chabazite and in sample 4 of the synthetic zeolite, respectively. For chabazite there is a continuous asymptotic decrease in ΔH as x increases (Barrer and Ibbitson, *loc. cit.*; Barrer, 1938, *loc. cit.*), while for both samples of the synthetic sorbent the ΔH–x curve shows a tendency

FIG. 5.



Variation of sorption heat with amount sorbed for methane, ethane, propane, and oxygen on the new mineral.

to be divided into two parts. This behaviour could mean that there are mainly two kinds of site available in this sorbent, but a continual variability in the sites in chabazite.

In Fig. 5(*a*), the ΔH–x curves cross for the hydrocarbons at larger values of x. This apparently surprising behaviour is considered, however, to be due to the smaller amount of the larger molecule C_3H_8 needed to saturate the interstitial sorption volume than of the smaller molecules C_2H_6 or CH_4. It has been pointed out (Barrer and Ibbitson, *loc. cit.*) that if two chain molecules x_1 and x_2 of lengths L_1 and L_2 are occluded in a zeolite, the relative saturation values shown will be approximated by

$$\frac{\text{Saturation value of } x_1}{\text{Saturation value of } x_2} = \frac{L_2}{L_1}$$

The appropriate relative dimensions of CH_4, C_2H_6, and C_3H_8 stand in the ratio 0·735 : 1·00 : 1·18. According to the above relationship, if the amounts of methane, ethane, and propane are multiplied by 0·735, 1·00, and 1·18 respectively, these abscissæ are proportional to θ, the fraction of sites occupied, and the constant of proportionality is the same. This has been done in Fig. 5(*b*), when it is seen that the ΔH–θ curves will no longer cross.

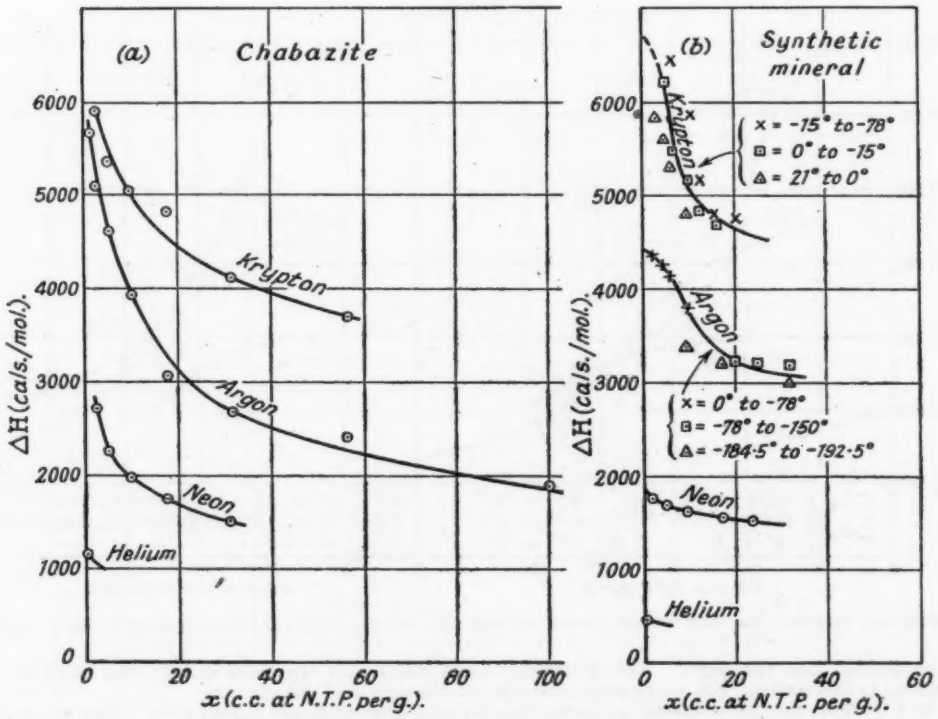
When the heats of sorption were measured at a series of temperatures, no definite evidence could be obtained of any systematic trend in ΔH with temperature, apart from random fluctuations due to experimental inaccuracy (Table II). The experimental accuracy is of the order of $\pm$ 600 cals. A similar insensitiveness of ΔH to temperature has been noted in other studies (Barrer and Ibbitson, *loc. cit.*; Barrer, 1938, *loc. cit.*).

TABLE II.

Sorption heats of C_3H_8 *in sample* 1 *of synthetic zeolite at different temperatures* (in °K.)

Amount sorbed, c.c. at N.T.P./g.	ΔH (cals./mol. sorbed). 293—343°.	343—513°.	513—553°.	553—593°.
3·44	—	—	—	17,300
4·35	—	—	17,700	16,800
5·00	—	—	17,300	16,100
6·90	—	—	16,900	15,400
8·64	—	—	15,200	13,700
10·9	—	9,330	11,300	10,700
13·7	—	8,160	8,200	7,200
17·3	8,330	6,950	6,700	—
21·7	6,560	5,700	—	—
26·1	5,000	—	—	—

FIG. 6.



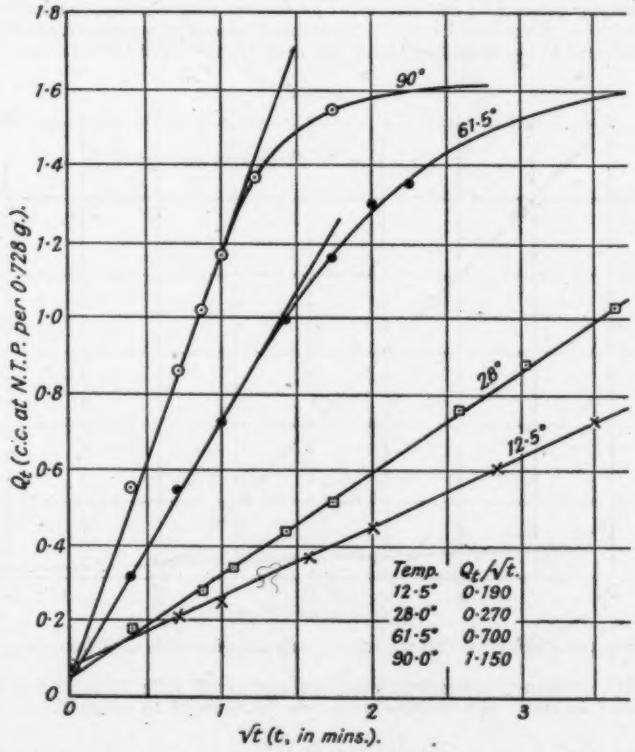
Variation of sorption heat with amount sorbed for the noble gases on (a) *natural chabazite,* (b) *new mineral.*

Some calculations of the standard free energies and thence entropies of occlusion in typical instances, by methods already given (Barrer and Ibbitson, *loc. cit.*; Barrer, *Trans. Faraday Soc.*, 1944, **40**, 374), led to the conclusion that the sorbate molecules behave not very differently from three-dimensional oscillators in both sorbents. Thus they may possess an amount of freedom comparable with liquids when sorbed interstitially.

Kinetics of Sorption.—An investigation of the kinetics of sorption of propane and of butane was made. These gases are sorbed slowly at room temperature, but more rapidly when the temperature is raised, by a process of diffusion within the crystal lattice. Over a considerable fraction of the total sorption the rate of uptake was a linear function of $\sqrt{t}$ (t = time), so the " parabolic " diffusion equation is clearly applicable. Fig. 7 shows this relationship, as well as the large temperature coefficient in the diffusion velocity. The small " foot " appearing along the axis of Q_t is to be interpreted as an initial rapid adsorption upon *external* surfaces of the powdered mineral, as distinct from the slower occlusion process. In accordance with this hypothesis, the foot diminishes somewhat as the temperature rises, corresponding to the exothermal character of adsorption. The slope $Q_t/\sqrt{t}$ of the linear portion of the

sorption rate curve is proportional to $C_0\sqrt{D}$, where D is the diffusion constant * and C_0 is the concentration of sorbate just inside the external surface of the sorbent particles. Now C_0 for the exothermal sorption of propane decreases, if anything, as the temperature rises, but nevertheless the overall rate of sorption increases with increasing temperature. It follows that the largest temperature coefficient resides in D. Table III gives values for $Q_t/\sqrt{t}$ for propane and *n*-butane; when $\log Q_t/\sqrt{t}$ is plotted against $1/T$, the points fall near to straight lines, with slopes corresponding to an apparent energy of activation, E_a, of 10·3 k.-cals. for propane and 11·4 k.-cals. for *n*-butane. There is no doubt, therefore, that sorption occurs by an activated diffusion process ($D = D_0 e^{-E/RT}$). The above apparent energies of activation may be smaller than the true energies, E, because the values of C_0, the concentration just inside the external surface of the particles of sorbent, will, if less than the saturation value, decrease as the temperature rises owing to the exothermal character of the occlusion.

FIG. 7.



Sorption kinetics of propane on the new mineral and the parabolic diffusion law.

TABLE III.

Temperature coefficients in the kinetics of sorption.

Propane.				*n*-Butane.			
Temp.	$Q_t/\sqrt{t}$.	Temp.	$Q_t/\sqrt{t}$.	Temp.	$Q_t/\sqrt{t}$.	Temp.	$Q_t/\sqrt{t}$.
12·5°	0·190	61·5°	0·700	17·5°	0·0333	86°	0·270
28	0·270	90·0	1·150	68	0·218	142	0·660

* If the diffusion equation $\partial C/\partial t = D(\partial C^2/\partial x^2)$ is integrated for the boundary condition $C = C_0$ at $x = 0$ for all t and the time interval is small enough for the inside of the particles not to have any appreciable content of occluded gas, then the solution, when the sorbing medium is initially gas free, is

$$C = C_0\left(1 - \frac{1}{\sqrt{\pi}}\int_0^{x/2\sqrt{Dt}} e^{-y^2}\,dy\right)$$

$$= C_0\left[1 - \frac{2}{\sqrt{\pi}}\left(\frac{x}{2\sqrt{Dt}} - \frac{x^3}{3\,.\,1'\,.\,(2\sqrt{Dt})^3} + \frac{x^5}{5\,.\,2'\,.\,(2\sqrt{Dt})^5} - \ldots\right)\right]$$

whence $$Q_t = -\int^t D\left(\frac{\partial C}{\partial x}\right)_{x=0} = C_0\frac{\sqrt{Dt}}{\sqrt{\pi}}$$

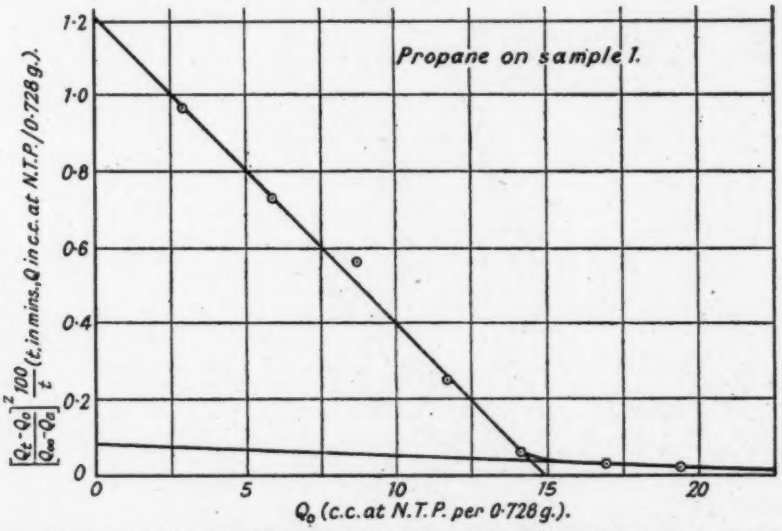
Ammonia, the noble gases, methane, ethane, oxygen, and nitrogen, by contrast to C_2H_6 and n-C_4H_{10}, were sorbed so rapidly that the rate-controlling step was almost certainly governed by the liberation of the heat of sorption, followed by the dissipation of this heat, and a settling in of the sorbed gas as the sorbent approached thermal equilibrium with its surroundings once more.

In a previous study of diffusion mechanisms (Barrer, *Trans. Faraday Soc.*, 1941, **37**, 590) it was pointed out that the diffusion " constant " D of a solute in interstitial solid solution within a homogeneous zeolitic sorbent should depend on the fraction θ of all available interstitial sites occupied, according to the expression $D = D_1(1 - \theta)$, so that when $\theta \to 1$, $D \to 0$. At constant C_0, the parabolic diffusion law becomes

$$(Q_t - Q_0)^2/t(Q_\infty - Q_0)^2 = kD_1(1 - \theta)$$

where Q_0, Q_∞, and Q_t are the amounts sorbed at time $t = 0$, $t = \infty$, and $t = t$, respectively, and k is a constant depending upon the particle size and number. The initial slopes of sorption rate curves according to the parabolic diffusion law should thus decrease linearly with θ, which is proportional to Q_0, the amount initially present in the sorbent. In testing this relation, successive doses of gas were admitted to the zeolite at room temperature, the sorbent becoming progressively filled with sorbed gas. The initial pressures, and so C_0, were kept constant, and the values of the left-hand side of the equation

FIG. 8.



Curve showing variation of diffusion coefficient in zeolitic solids with increasing saturation.

are given in Table IV. When this quotient is plotted against Q_0 (Fig. 8) the curve is seen to consist of two parts, suggesting two kinds of sorption site within the mineral to which there are different rates of

TABLE IV.

Q_0	2·92	5·92	8·73	11·64	14·40	16·94	19·40
Q_∞	5·92	8·73	11·64	14·50	17·68	19·88	22·35
$\left(\frac{Q_t - Q_0}{Q_\infty - Q_0}\right)^2 \times \frac{10^2}{t}$	0·96	0·73	0·56	0·25	0·057	0·0262	0·0156

access. The first group of sites requires about 15 c.c. of propane at N.T.P/0·728 g. of mineral to become saturated, and in this group sorption occurs much more rapidly than in the second group of sites. Some evidence, based upon the form of heat–charge curves particularly of hydrocarbons (*loc. cit.*, and Fig. 5) has already been given supporting the existence of two groups of sorption sites.

DISCUSSION.

In considering occlusion by zeolites it must be remembered that cations as well as sorbed molecules are simultaneously present in the same interstitial channels throughout the anionic network. Evidence has already been obtained which shows clearly that sorbate and cation are in close association (Barrer, *Trans. Faraday Soc.*, 1944, **40**, 555). The inhomogeneity of the sorbents, as revealed by the variation of ΔH with the charge of gas, can then be due to the following causes : (i) There may be at least two crystallographically distinct sets of interstices, each capable of occluding sorbate molecules. Each set then develops its own sorption potential, and the isotherm is the resultant of two or more isotherms of Langmuir type. (ii) There may be only one set of sites capable of accommodating sorbate molecules, but there may be partial

exchanges such as Na^+ by K^+, Ca^{++} by Ba^{++}, $2Na^+$ by Ca^{++}, and so on, the sorption potential then varying with the type of ion in occupation in the interstice. Such exchanges are already known to modify strongly the energetics of sorption (*idem, ibid.*). (iii) There may be room for more than one small molecule in the same interstices as the cation, but whereas the first molecule is in contact with the cation, others, for steric reasons, are displaced from the cation and therefore bound in a field of modified potential. (iv) At high interstitial concentrations, the sorbate molecules may interact strongly enough to produce clustering, with dilute and concentrated phases in equilibrium.

When ΔH is plotted as a function of x, the charge of gas, the data show, over the investigated values of x, the following behaviour. For " active " analcite (Barrer and Ibbitson, *loc. cit.*; Barrer, 1938, *loc. cit.*) there was only a small dependence of ΔH upon x, and the sorption sites were therefore comparatively uniform. In natural mordenite, and more especially in chabazite (*locc. cit.*, 1938, 1944), ΔH decreases continuously with increasing x, but here the known chemical heterogeneity of these minerals could offer one explanation of the behaviour in accordance with (ii) above. The synthetic mineral now investigated shows a rather more definite break in the ΔH–x curve, which might be ascribed to the presence of two similar sets of interstitial sites. In this connection the kinetic evidence of Fig. 8 is the most convincing.

A tendency towards clustering of sorbate molecules has not yet been observed in gas–zeolite systems, and would be revealed by an *increase* in ΔH for larger values of x. Such behaviour was noted by Orr (*Proc. Roy. Soc.*, 1939, **173**, *A*, 349) when noble gases were sorbed on external surfaces of alkali halide crystals; while clustering of hydrogen atoms is well established in H_2–Pd systems and leads under certain conditions to an equilibrium between α- and β-phases (*e.g.*, Lacher, *ibid.*, 1937, **161**, *A*, 525); and evidence for a variety of sub-phases has been adduced by Jura and Harkins (*J. Amer. Chem. Soc.*, 1946, **68**, 1941) and by Jura, Loeser, Basford, and Harkins (*J. Chem. Physics*, 1945, **13**, 535). First- or second-order phase changes may therefore eventually be found in the present zeolitic solid solutions, where only physical interactions occur.

A second point of interest arises in applying to molecular-sieve zeolites the rule of Gurwitsch (*J. Russ. Phys. Chem. Soc.*, 1915, **47**, 805)—that the saturation volumes expressed as c.c. of liquid sorbate are the same for all sorbates in a given sorbent. This rule may be considered valid only for sorbents with wide, easily accessible pores. It has been shown, however, that in several gel sorbents the saturation quantities expressed as moles decrease nearly inversely as the molecular volume of the sorbate, and this behaviour has been interpreted in terms of a range in pore sizes resulting in a continuous but only partial molecular-sieve action (Foster, *Nature*, 1946, **157**, 340; Broad and Foster, *J.*, 1945, 366). The zeolitic molecular sieves, however, constitute a third group. For very small molecules Gurwitsch's rule is a good approximation. For molecules of intermediate size an interesting behaviour appears. Some sorbates which are copiously occluded, may have molecular volumes equal to or greater than the molecular volumes of other sorbates which are not sorbed at all. For example, on the one hand *n*-heptane, *n*-pentane, and *n*-butane are copiously occluded by suitably activated chabazite, and on the other hand *iso*pentane, *iso*butane, chloroform, and benzene are totally excluded (Barrer, 1945, *loc. cit.*; Barrer and Ibbitson, *loc. cit.*). This is because it is molecular shape rather than molecular volume which decides whether sorption can occur. Clearly, in this intermediate range of molecular dimensions, it is quite impossible to apply Gurwitsch's rule indiscriminately. Finally come very large molecules towards which zeolites do not behave as sorbents.

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35. *Acyl Derivatives of* p-*Aminobenzenesulphonylguanidine.*

By P. R. CARTER, D. H. HEY, and D. S. MORRIS.

Various acyl derivatives of *p*-amino- and *p*-nitro-benzenesulphonylguanidine are prepared. Acetylation of *p*-aminobenzenesulphonylguanidine gives *p*-acetamidobenzenesulphonylguanidine and p-*acetamidobenzenesulphonylacetylguanidine*, and the latter is also prepared from *p*-acetamidobenzenesulphonyl chloride and acetylguanidine and from p-*acetamidobenzenesulphonylacetylmethyl*isothiourea and ammonia. The corresponding *mono-* and *di-propionyl* derivatives are also prepared. p-*Aminobenzenesulphonylacetylguanidine*, p-*aminobenzenesulphonylbenzoylguanidine*, and p-*aminobenzenesulphonyldibenzoylguanidine* are prepared by the reduction of the corresponding p-*nitro*-compounds. Condensation of *p*-acetamidobenzenesulphonylacetylguanidine with ethyl acetoacetate gives 6-*hydroxy*-2-p-*acetamidobenzenesulphonamido*-4-*methylpyrimidine*.

Of the various chemotherapeutic agents of the sulphonamide group, *p*-aminobenzenesulphonylguanidine (sulphaguanidine) is one of the most effective in the treatment of certain pathogenic infections of the intestinal tract. Divinskii and Vorob'eva (*Compt. rend. Acad. Sci. U.R.S.S.*, 1942, **36**, 203) observed that many sulphonamides are acetylated *in vivo* to give the less toxic acetyl derivatives, and showed that *p*-acetamidobenzenesulphonylguanidine is highly active physiologically and practically non-toxic. Northey (*Chem. Reviews*, 1940, **27**, 173) has also pointed out that some N^1-acylsulphanilamides are more active than sulphanilamide, and among these, N^1-acetylsulphanilamide (albucid, sulphacetamide), N^1-benzoylsulphanilamide (sulphabenzamide), and N^1-dimethylacrylylsulphanilamide (irgamide) have received considerable attention. Since the preparations described below were completed, Rose and Tuey (*J.*, 1946, 82) have reported that 2-(*p*-acetamidobenzenesulphonamido)-4 : 6-dimethoxypyrimidine, although devoid of *in vitro* activity, is almost as effective *in vivo* as the highly active free amine, 2-(*p*-aminobenzenesulphonamido)-4 : 6-dimethoxypyrimidine, and have shown that this is due to rapid deacetylation in the body. There would thus appear to be a strong case for the examination of the *in vivo* activity of various acylated derivatives of *p*-aminobenzenesulphonylguanidine. *p*-Aminobenzenesulphonylguanidine possesses in all four basic centres which are capable of acylation. In the absence of conclusive evidence to the contrary the acyl groups in di- and tri-acylated *p*-aminobenzenesulphonylguanidines are regarded as being attached to different basic groups. The solubility of *p*-acetamidobenzenesulphonylacetylguanidine in cold aqueous sodium hydroxide may be taken as evidence of the presence of the group $\cdot SO_2 \cdot NH \cdot C\vdots$.

Acetylation of *p*-aminobenzenesulphonylguanidine under mild conditions afforded *p*-acetamidobenzenesulphonylguanidine (I), identical with the product obtained from the condensation of *p*-acetamidobenzenesulphonyl chloride with guanidine as described by Marshall *et al.* (*Johns Hopkins Hosp. Bull.*, 1940, **67**, 163). Acetylation of *p*-aminobenzenesulphonylguanidine under more vigorous conditions afforded p-*acetamidobenzenesulphonylacetylguanidine* (III), the structure of which was confirmed by the preparation of identical compounds by (*a*) acetylation of *p*-acetamidobenzenesulphonylguanidine and (*b*) condensation of *p*-acetamidobenzenesulphonyl chloride with acetylguanidine. It has been found that *p*-acetamidobenzenesulphonylguanidine may also be prepared by heating urea with *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (II), which in turn may be formed by condensation of *p*-acetamidobenzenesulphonyl chloride with methyl*iso*thiourea sulphate or chloride in cold aqueous acetone with the gradual addition of alkali. After the completion of this work a similar method of preparation was described by Haworth, Rose, and Swain (B.P. 554,975 : see also Birtwell, Haworth, Rose, Swain, and Vasey, *J.*, 1946, 493). *p*-Acetamidobenzenesulphonylmethyl*iso*thiourea has also been mentioned by Winnek, Anderson, Marson, Faith, and Roblin (*J. Amer. Chem. Soc.*, 1942, **64**, 1682) but no details were given.* Acetylation of *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (II) gave p-*acetamidobenzenesulphonylacetylmethylisothiourea* (IV), which on treatment with ammonia gave methylthiol and *p*-acetamidobenzenesulphonylacetylguanidine (III). Partial hydrolysis of *p*-acetamidobenzenesulphonylacetylguanidine under acid or alkaline conditions afforded only *p*-acetamidobenzenesulphonylguanidine with no evidence of the formation of the isomeric p-*aminobenzenesulphonylacetylguanidine* (VII) : the latter compound was prepared by the catalytic reduction under neutral conditions of p-*nitrobenzenesulphonylacetylguanidine* (VI), prepared either by condensation of *p*-nitrobenzenesulphonyl chloride with acetylguanidine or by acetylation of *p*-nitrobenzenesulphonylguanidine (V). Acetylation of *p*-aminobenzenesulphonylacetylguanidine gave the expected *p*-acetamidobenzenesulphonylacetylguanidine referred to above. These reactions may be represented as shown on p. 145.

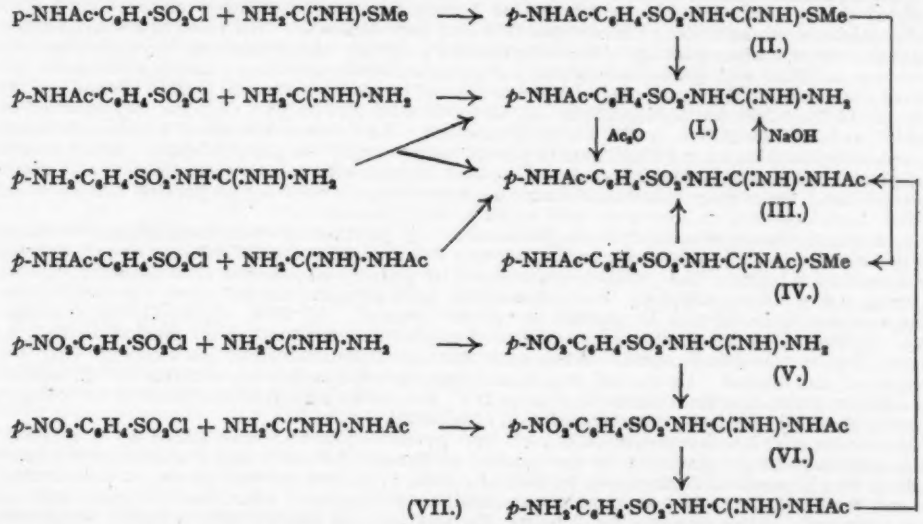
The corresponding *mono-* and *di-propionyl* derivatives of *p*-aminobenzenesulphonylguanidine were prepared in similar manner, and treatment of *p*-acetamidobenzenesulphonylguanidine with propionic anhydride gave p-*acetamidobenzenesulphonylpropionylguanidine*.

Benzoylation of *p*-nitrobenzenesulphonylguanidine with an excess of benzoic anhydride gave p-*nitrobenzenesulphonyldibenzoylguanidine*, but with a molecular proportion p-*nitrobenzenesulphonylbenzoylguanidine* was obtained. Both the mono- and the di-benzoyl derivative were reduced catalytically to p-*aminobenzenesulphonylbenzoylguanidine* and p-*aminobenzenesulphonyldibenzoylguanidine*, respectively.

Several methods have been reported by means of which sulphanilylaminopyrimidines may be

* Cox, (*J. Org. Chem.*, 1942, **7**, 307) had reported a similar method of preparation from arylsulphonylmethyl*iso*thioureas, but at the time of this work this paper was not available in Great Britain and was only seen in abstract (*Chem. Abstracts*, 1942, **36**, 6146). Acyl derivatives of *p*-aminobenzenesulphonylalkyl*iso*thioureas are also described by Kereszty and Wolf (Hungarian Patent, 127,731 ; *Chem. Abs.*, 1942, **36**, 2270) and by Bergmann, Israelashvili, and Weinberg, *J. Amer. Chem. Soc.*, 1946, **68**, 761).

prepared by the condensation of *p*-nitro-, *p*-amino-, or *p*-acetamido-benzenesulphonylguanidine with 1 : 3-diketones and similar compounds. The condensation of *p*-acetamidobenzenesul-



phonylacetylguanidine with ethyl acetoacetate could give rise to either the ethyl ester of 2-*p*-acetamidobenzenesulphonamido-4 : 6-dimethylpyrimidine-5-carboxylic acid with elimination of water, or 2-*p*-acetamidobenzenesulphonamido-4-hydroxy-6-methylpyrimidine with elimination of water and ethyl acetate; but it was found that when the above two reagents were heated together at 150° in presence of zinc chloride the latter product was in fact formed. This compound was subsequently described by Rose and Swain (*J.*, 1945, 691), who prepared it by heating *p*-acetamidobenzenesulphonylguanidine with ethyl acetoacetate (cf. Ganapathi, Deliwala, and Shirsat, *Proc. Indian Acad. Sci.*, 1942, **16***A*, 115).

Experimental.

p-Acetamidobenzenesulphonylguanidine was prepared from *p*-acetamidobenzenesulphonyl chloride (Smiles and Stewart, *Org. Synth.*, Coll. Vol. I, Second Ed., 8) and guanidine nitrate as described by Marshall *et al.* (*loc. cit.*). Crystallisation from 50% acetic acid gave the monohydrate in colourless plates, m. p. 264°. The *p*-acetamidobenzenesulphonyl chloride was purified by the method of Pence and Winter (*J. Amer. Chem. Soc.*, 1939, **61**, 2977). Hydrolysis with 6N-hydrochloric acid as described by Marshall *et al.* (*loc. cit.*) gave *p*-aminobenzenesulphonylguanidine, which separated from 95% alcohol in fine colourless needles, which softened at 168—178°, and melted at 189°.

Action of Acetic Anhydride on p-*Aminobenzenesulphonylguanidine.*—(a) Acetic anhydride (50 c.c.) was added slowly with shaking to a solution of *p*-aminobenzenesulphonylguanidine (21·4 g.) in warm dry pyridine (60 c.c.). Heat was developed, and a crystalline deposit separated. The mixture was cooled and filtered. Crude *p*-acetamidobenzenesulphonylguanidine (12·3 g., m. p. 262°) was collected; after crystallisation from 50% acetic acid it melted at 264°, both alone and on admixture with the compound prepared as above from *p*-acetamidobenzenesulphonyl chloride and guanidine nitrate.

(b) Acetic anhydride (50 c.c.) was added to *p*-aminobenzenesulphonylguanidine (21·4 g.) in warm dry pyridine (60 c.c.) as described above. The mixture was then boiled under reflux for 3 hours, during which the solid dissolved to give a clear brown solution. After removal of pyridine and excess of acetic anhydride under reduced pressure, the glassy residue was crystallised from 50% acetic acid (200 c.c.). A second crystallisation from the same solvent (or from ethyl alcohol) gave p-*acetamidobenzenesulphonylacetylguanidine* (21·2 g.) in colourless needles (or prisms from alcohol), m. p. 261° (Found: C, 44·6; H, 4·8. $C_{11}H_{14}O_4N_4S$ requires C, 44·3; H, 4·7%). The same compound (13·9 g.) was obtained when *p*-acetamidobenzenesulphonylguanidine (25·6 g.) was boiled under reflux for two hours with dry pyridine (60 c.c.) and acetic anhydride (40 c.c.). The same compound was also obtained when a mixture of *p*-acetamidobenzenesulphonyl chloride (1·86 g.) and acetylguanidine (0·81 g.), prepared from free guanidine and ethyl acetate as described by Traube (*Ber.*, 1910, **43**, 3588), in dry pyridine (10 c.c.) was boiled gently under reflux for 20 minutes and then kept at 100° for 2 hours. The cold mixture was filtered and the filtrate was evaporated to dryness in a vacuum. Trituration of the oily residue with ice-water (50 c.c.) gave a solid product which was recrystallised first from 50% acetic acid (charcoal) and then from ethyl alcohol. *p*-Acetamidobenzenesulphonylacetylguanidine was obtained, as above, in colourless prisms, m. p. 261°.

When *p*-acetamidobenzenesulphonylacetylguanidine (2·98 g.) was added to a cold solution of sodium hydroxide (1·2 g.) in water (10 c.c.), the solid dissolved, and after standing for 6 hours *p*-acetamidobenzenesulphonylguanidine, m. p. and mixed m. p. 264°, separated. Hydrolysis with boiling N/10-hydrochloric acid for ½ hour was very incomplete, but boiling under reflux for 2 hours, followed by neutralisation and

concentration, gave *p*-aminobenzenesulphonylguanidine, m. p. and mixed m. p. 189° after crystallisation from alcohol.

N-(p-*Acetamidobenzenesulphonyl*)-S-*methylisothiourea*.—Aqueous sodium hydroxide (10 g. in 20 c.c.) was added slowly with stirring to a solution of *p*-acetamidobenzenesulphonyl chloride (23·3 g.) and methyl*iso*thiourea sulphate (14 g.) in acetone (100 c.c.) kept below 0°. (In place of methyl*iso*thiourea sulphate the corresponding quantity of the chloride may be used.) After standing overnight the reaction mixture was acidified with glacial acetic acid. *p*-Acetamidobenzenesulphonylmethyl*iso*thiourea (11 g.) separated; it crystallised from alcohol or aqueous alcohol in small needles, m. p. 235° (Found: C, 42·4; H, 4·8; N, 14·75. Calc. for $C_{10}H_{13}O_3N_3S_2$: C, 41·9; H, 4·5; N, 14·6%). Cox (*loc. cit.*) reported m. p. 230—232°, and B.P. 554,975 m. p. 236° for this compound. An intimate mixture of *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (1 g.) and urea (1 g.) was heated at 150° for about 2 hours. When liberation of methylthiol had ceased, the melt was allowed to cool, treated with boiling water (25 c.c.) and charcoal, and filtered hot. On cooling, *p*-acetamidobenzenesulphonylguanidine (0·5 g.) separated in white needles, m. p. 264° both alone and on admixture with an authentic specimen.

p-*Acetamidobenzenesulphonylacetylmethylisothiourea*.—A mixture of *p*-acetamidobenzenesulphonylmethyl*iso*thiourea (1·7 g.), anhydrous sodium acetate (0·5 g.), and acetic anhydride (10 c.c.) was boiled under reflux for 3 hours. The product was isolated by pouring on ice, and after standing, the white precipitate (1·5 g.) was collected. Recrystallisation from aqueous alcohol gave p-*acetamidobenzenesulphonylacetylmethylisothiourea* in needles, m. p. 92° (Found: N, 11·4. $C_{12}H_{15}O_4N_3S_2$ requires N, 11·4%). A stream of dry ammonia was passed through this compound (1 g.), heated at 210°, until evolution of methylthiol had ceased. When cold, the melt was dissolved in hot water (20 c.c.), boiled with charcoal, and filtered. On cooling, *p*-acetamidobenzenesulphonylacetylguanidine (0·7 g.) separated, which after crystallisation from alcohol had m. p. 261°, both alone and on admixture with the compound prepared as described above by direct acetylation of sulphanilylguanidine.

p-*Nitrobenzenesulphonylacetylguanidine*.—(a) Dry pyridine (10 c.c.) was added to a mixture of acetylguanidine (0·85 g.), prepared by the method of Traube (*loc. cit.*), and *p*-nitrobenzenesulphonyl chloride (1·88 g.), prepared as described by Bell (*J.*, 1928, 2776) and purified by the procedure used by Pence and Winter (*loc. cit.*) for *p*-acetamidobenzenesulphonyl chloride. Heat was developed, and a clear solution obtained. After standing for 2 hours, the mixture was filtered from a highly water-soluble crystalline deposit, and the filtrate evaporated to dryness on the water-bath under reduced pressure. Trituration of the residue with water gave p-*nitrobenzenesulphonylacetylguanidine* in low yield; after several crystallisations from alcohol, this was obtained in colourless prisms, m. p. 230—231° (Found: C, 37·9; H, 3·4. $C_9H_{10}O_5N_4S$ requires C, 37·8; H, 3·5%).

(b) *p*-Nitrobenzenesulphonyl chloride (2·21 g.) was added gradually with shaking to a solution of acetylguanidine acetate (1·61 g.), prepared by the method of Korndörfer (*Arch. Pharm.*, 1903, **241**, 467), in dry pyridine (20 c.c.). The brown solution was heated at 100° for 15 minutes, after which the solvent was removed under reduced pressure and the residue triturated with ice-water. Crystallisation several times from alcohol gave *p*-nitrobenzenesulphonylacetylguanidine in low yield, m. p. 230—231°, both alone and on admixture with the compound prepared above by method (a).

(c) *p*-Nitrobenzenesulphonylguanidine (14·6 g.), prepared from *p*-nitrobenzenesulphonyl chloride and guanidine nitrate in the same manner as was used by Marshall *et al.* (*loc. cit.*) for the preparation of *p*-acetamidobenzenesulphonylguanidine, was heated under reflux with an excess of acetic anhydride (50 c.c.) for 2 hours. The crystalline deposit which separated on cooling was collected and washed with alcohol and ether. Recrystallisation from alcohol gave *p*-nitrobenzenesulphonylacetylguanidine (7·5 g.) in colourless prisms, m. p. 230—231°, both alone and on admixture with the sample prepared by methods (a) and (b) above.

p-Nitrobenzenesulphonylacetylguanidine is sparingly soluble in cold water, but dissolves in cold dilute sodium hydroxide to give a colourless solution which turns yellow and deposits *p*-nitrobenzenesulphonylguanidine, m. p. 224°, on standing.

p-*Aminobenzenesulphonylacetylguanidine*.—Finely powdered *p*-nitrobenzenesulphonylacetylguanidine (1 g.) was suspended in absolute alcohol (250 c.c.) and shaken with Raney nickel (1 g.) in an atmosphere of hydrogen at room temperature and pressure. The theoretical volume of hydrogen was absorbed in 6 hours. The mixture was warmed and filtered, and the filtrate concentrated to 50 c.c. by heating under reduced pressure at 40°. On cooling to 0° p-*aminobenzenesulphonylacetylguanidine* (0·6 g.) separated in very pale yellow prisms, m. p. 210°, after recrystallisation from alcohol (Found: C, 42·4; H, 4·9. $C_9H_{12}O_3N_4S$ requires C, 42·2; H, 4·7%). This compound is readily hydrolysed in alkaline media but is stable when suspended in a buffer solution at pH 2·4 at 41°. On being boiled with an excess of acetic anhydride for 2 hours and poured into water, *p*-acetamidobenzenesulphonylacetylguanidine was obtained, m. p. and mixed m. p. 261° after crystallisation from alcohol. Reduction of *p*-nitrobenzenesulphonylacetylguanidine by boiling with iron filings and calcium chloride in aqueous alcohol afforded *p*-aminobenzenesulphonylguanidine.

Action of Propionic Anhydride on p-*Aminobenzenesulphonylguanidine*.—(a) Propionic anhydride (2·6 g.) was added to a hot solution of the guanidine (4·28 g.) in dry pyridine (25 c.c.). After standing overnight at room temperature, the mixture was evaporated to dryness under reduced pressure and the white solid residue was crystallised twice from boiling water (100 c.c.). p-*Propionamidobenzenesulphonylguanidine* (3·6 g.) was obtained in colourless plates, m. p. 195—196° (Found: C, 41·8; H, 5·7. $C_{10}H_{14}O_3N_4S,H_2O$ requires C, 41·7; H, 5·55%).

(b) *p*-Aminobenzenesulphonylguanidine (4·28 g.) was boiled under reflux for 3 hours with dry pyridine (25 c.c.) and propionic anhydride (7·8 g.). The clear brown solution was evaporated to dryness under reduced pressure. Crystallisation of the residual glass from 50% acetic acid (50 c.c.) (charcoal) gave p-*propionamidobenzenesulphonylpropionylguanidine* (2·7 g.) in colourless needles, which softened at 240° and melted at 247° (Found: C, 47·9; H, 5·5. $C_{13}H_{18}O_4N_4S$ requires C, 47·85; H, 5·5%). The same compound was obtained when *p*-propionamidobenzenesulphonylguanidine was heated under reflux for 2 hours with excess of propionic anhydride, followed by evaporation on the water-bath under reduced pressure and crystallisation of the residue as before.

p-*Acetamidobenzenesulphonylpropionylguanidine.*—*p*-Acetamidobenzenesulphonylguanidine (2·56 g., 0·01 mol.) was boiled under reflux overnight with dry pyridine (15 c.c.) and propionic anhydride (2·6 g., 0·02 mol.). On cooling, the unchanged guanidine which separated (m. p. and mixed m. p. 264°), was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure on the water-bath. The residual oil was taken up in warm absolute alcohol. Addition of water precipitated p-*acetamidobenzenesulphonylpropionylguanidine*, which crystallised from dilute acetic acid in colourless needles, m. p. 203° (Found : C, 45·75; H, 5·3. $C_{12}H_{16}O_4N_4S$ requires C, 46·15; H, 5·1%).

Action of Benzoic Anhydride on p-*Nitrobenzenesulphonylguanidine.*—(a) A mixture of *p*-nitrobenzenesulphonylguanidine (4·88 g.) and benzoic anhydride (18 g.), prepared as described by Kaufmann and Luterbacher (*Ber.*, 1909, **42**, 3483), was heated at 150—160° for 4 hours. When cold, the melt set to a solid mass, which was powdered and boiled under reflux with dry ether (500 c.c.). The insoluble material was collected, boiled with alcohol, cooled, and filtered. The insoluble p-*nitrobenzenesulphonyldibenzoylguanidine* (4·5 g.) separated from absolute alcohol (*ca.* 3000 c.c.) in colourless needles, m. p. 197° (Found : C, 56·1; H, 3·4. $C_{21}H_{16}O_6N_4S$ requires C, 55·8; H, 3·5%).

(b) A mixture of *p*-nitrobenzenesulphonylguanidine (19·5 g.) and benzoic anhydride (22·0 g.) was heated at 150° for 3 hours and then at 200° for 1 hour. The melt, which solidified on cooling, was powdered and extracted with boiling dry ether, and the insoluble residue was crystallised from absolute alcohol (7500 c.c.). p-*Nitrobenzenesulphonylbenzoylguanidine* (17·0 g.) separated in colourless plates, m. p. 227° (Found : C, 48·4; H, 3·4. $C_{14}H_{12}O_5N_4S$ requires C, 48·3; H, 3·45%). The same compound was obtained in small yield from *p*-nitrobenzenesulphonylguanidine and benzoyl chloride by boiling under reflux for 6 hours in pyridine solution, followed by evaporation of the solvent and repeated crystallisation of the residue from absolute alcohol.

p-*Aminobenzenesulphonylbenzoylguanidine.*—A suspension of finely powdered *p*-nitrobenzenesulphonylbenzoylguanidine (1 g.) and Raney nickel (1 g.) in absolute alcohol (300 c.c.) was shaken with hydrogen at room pressure and temperature. When the theoretical volume of hydrogen had been absorbed the solution was warmed and filtered (charcoal). Concentration of the filtrate afforded needles of p-*aminobenzenesulphonylbenzoylguanidine*, which after further crystallisation from alcohol melted at 249° (Found : C, 53·2; H, 4·4. $C_{14}H_{14}O_3N_4S$ requires C, 52·8; H, 4·4%); it is stable at 41° when suspended in a buffer solution at pH 2·4.

p-*Aminobenzenesulphonyldibenzoylguanidine.*—*p*-Nitrobenzenesulphonyldibenzoylguanidine was catalytically reduced as described above for the corresponding monobenzoyl derivative. Recrystallisation of the product from absolute alcohol gave p-*aminobenzenesulphonyldibenzoylguanidine* in very pale yellow needles, m. p. 225° (Found : C, 59·6; H, 4·2. $C_{21}H_{18}O_4N_4S$ requires C, 59·7; H, 4·3%). Hydrolysis with 2N-sodium hydroxide for 2 hours at 100° gave *p*-aminobenzenesulphonylguanidine.

2-p-*Acetamidobenzenesulphonamido-4-hydroxy-6-methylpyrimidine.*—A mixture of *p*-acetamidobenzenesulphonylacetylguanidine (3 g.), freshly fused powdered zinc chloride (7 g.), and ethyl acetoacetate (15 c.c.) was heated in an oil-bath at 150° for 3 hours in a flask fitted with an air condenser and a calcium chloride guard-tube. When cold, the mass was extracted with water and then with ether. The insoluble residue (2·4 g.) was crystallised from 50% acetic acid and finally from aqueous alcohol. The pyrimidine was obtained in prisms, m. p. 277° (Found : C, 48·2; H, 4·5; N, 17·1. Calc. for $C_{13}H_{14}O_4N_4S$: C, 48·45; H, 4·35; N, 17·4%). A specimen of the same compound was prepared by heating *p*-acetamidobenzenesulphonylguanidine with excess of ethyl acetoacetate at 160° for 2 hours according to the method of Rose and Swain (*loc. cit.*). No depression in m. p. was obtained when the products prepared by the two methods were mixed.

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36. *The Action of Chlorine on Aqueous Solutions of Ammonium Sulphinates.*

By P. R. Carter and D. H. Hey.

The action of chlorine or sodium hypochlorite on solutions of the ammonium salts of *p*-acetamidobenzenesulphinic acid, *p*-nitrobenzenesulphinic acid and ω-acetamido-*p*-toluenesulphinic acid gives the corresponding sulphonamides. Application of the reaction to the salts of these sulphinic acids with heterocyclic primary amines is less successful owing to side reactions, although 2-(*p*-acetamidobenzenesulphonamido)pyridine and 2-(*p*-nitrobenzenesulphonamido)pyridine are obtained in low yield from the action of chlorine on solutions of the salts of 2-aminopyridine with the appropriate sulphinic acid.

Therapeutically valuable sulphonamides have been prepared by the oxidation of sulphenamides (B.P. 550,446, 551,205, 551,206, 551,207, 557,055 and 559,384), and sulphinamides (Morren and Lehmann, *J. Pharm. Belg.*, 1942, **1**, 127). It has been reported in D.R.-P. 122,567 (Basler Chemische Fabrik) that certain aromatic sulphonamides can be obtained by passing chlorine into an aqueous alcoholic ammoniacal solution of the sulphinic acid in presence of excess of ammonia or sodium carbonate. No attempts appear to have been made to apply this reaction to the preparation of therapeutically useful sulphonamides.

p-Acetamidobenzenesulphinic, *p*-nitrobenzenesulphinic, and ω-acetamido-*p*-toluenesulphinic acid were prepared from the corresponding sulphonyl chlorides and aqueous sodium sulphite, and it is now shown that the action of chlorine or sodium hypochlorite on the ammonium salts of these acids in aqueous alcohol at 35—40° gives the corresponding sulphonamides, namely, *p*-acetamidobenzenesulphonamide, *p*-nitrobenzenesulphonamide, which was reduced to *p*-aminobenzenesulphonamide, and ω-acetamido-*p*-toluenesulphonamide respectively. Application of the reaction to salts of sulphinic acids with heterocyclic primary amines gave less satisfactory results. Treatment of 2-aminopyridine *p*-acetamidobenzenesulphinate with chlorine, under the conditions used successfully with the above ammonium sulphinates, gave in low yield 2-(*p*-acetamidobenzenesulphonamido)pyridine, which was hydrolysed to 2-(*p*-aminobenzenesulphonamido)pyridine, the main product being acetanilide-*p*-disulphone. Various modifications in the experimental conditions, as described in the experimental section, led to an increase in the yield of the sulphonamidopyridine from 5 to 18%. In similar manner the action of chlorine on the salt of *p*-nitrobenzenesulphinic acid with 2-aminopyridine gave 2-(*p*-nitrobenzenesulphonamido)pyridine. Subsequent experiments with the sulphinic acid salts of other heterocyclic primary amines, *e.g.*, 2-aminothiazole, 2-aminopyrimidine, and 2-amino-4 : 6-dimethylpyrimidine, failed to yield the corresponding sulphonamides but gave mainly water-soluble products, which probably consisted of salts of the corresponding sulphonic acids, and in some cases the disulphone.

According to Otto and Ostrop (*Annalen*, 1867, **141**, 372) arylsulphinic acids are converted into the corresponding sulphonyl chlorides or bromides by warming with aqueous chlorine or bromine. It is considered possible that the action of chlorine on the ammonium sulphinates gives the corresponding sulphonyl chlorides, but a direct oxidation mechanism is also possible, especially since the disulphone, which is formed as a by-product in some cases, is known to be obtained when sulphinic acids are oxidised in acetic acid solution with potassium permanganate (Child and Smiles, *J.*, 1926, 2696). On the other hand, the same disulphone may result from the interaction of the sulphonyl chloride with the sulphinic acid as represented below (reaction *b*, iii). The active agent is almost certainly hypochlorous acid since the reaction does not proceed under anhydrous conditions, and aqueous sodium hypochlorite can replace aqueous chlorine in these reactions. The overall reaction may be represented by the following equations in which the formation of the sulphonamide is but one of three simultaneous reactions :

$$(a) \quad R\cdot SO_2H + HOCl \longrightarrow R\cdot SO_2Cl + H_2O$$

$$(b)\ (i) \quad R\cdot SO_2Cl + H_2O \longrightarrow R\cdot SO_2\cdot OH + HCl$$

$$(ii) \quad R\cdot SO_2Cl + R'\cdot NH_2 \longrightarrow R\cdot SO_2\cdot NHR' + HCl$$

$$(iii) \quad R\cdot SO_2Cl + R\cdot SO_2H \longrightarrow R\cdot SO_2\cdot SO_2R + HCl$$

Experimental.

p-Acetamidobenzenesulphinic acid, m. p. 155° (decomp.), was prepared in 60% yield from *p*-acetamidobenzenesulphonyl chloride and sodium sulphite as described by Smiles and Bere (*Org. Synth.*, Coll. Vol. I, 7).

p-Nitrobenzenesulphinic acid was prepared in 50% yield from diazotised *p*-nitroaniline and sulphur dioxide in presence of copper, according to the general procedure of Hanke (*J. Amer. Chem. Soc.*, 1923, **45**, 1325) for the preparation of *p*-chlorobenzenesulphinic acid. The acid separated from water in pale yellow needles which sintered at 136° and had m. p. 160° (decomp.), in agreement with Zincke and Lenhardt (*Annalen*, 1913, **400**, 15). *p*-Nitrobenzenesulphinic acid was also prepared in 55% yield from *p*-nitrobenzenesulphonyl chloride and sodium sulphite by the same procedure as used for the preparation of *p*-acetamidobenzenesulphinic acid. The *p*-nitrobenzenesulphonyl chloride was prepared by the method of Bell (*J.*, 1928, 2776).

*ω-Acetamido-*p*-toluenesulphinic Acid.*—Crude ω-acetamido-*p*-toluenesulphonyl chloride, prepared from acetbenzylamide (20 g.) as described by Bergeim and Braker (*J. Amer. Chem. Soc.*, 1944, **66**, 1459), was shaken for 2 hours with a cold solution of crystalline sodium sulphite (67·2 g.) in water (135 c.c.) with the periodical addition of small quantities of 50% aqueous sodium hydroxide to keep the mixture just alkaline. The cold filtered solution was carefully acidified with an ice-cold solution of sulphuric acid (40 g.) in water (40 c.c.) and the precipitated sulphinic acid collected at the pump, washed with ice–water, and placed in a vacuum desiccator over potassium hydroxide. The crude product containing sodium sulphate was recrystallised from pre-heated water (200 c.c.) and ω-acetamido-*p*-toluenesulphinic acid (6·9 g.) separated in colourless plates, m. p. 138° (Found : C, 50·6; H, 5·3. Calc. for $C_9H_{11}O_3NS$: C, 50·7; H, 5·2%). Subsequent to the completion of this work this acid has been described by Jensen and Schmith (*Z. physiol. Chem.*, 1944, **280**, 35) and by Dewing (*J.*, 1946, 467), who give m. p. 137—138° and 148° respectively. More recently it has also been described by Boots Pure Drug Co., Koebner and Short (B.P. 584,584), who record m. p. 139—140°.

Action of Chlorine on Ammonium p-*Acetamidobenzenesulphinate.*—Chlorine (450 c.c.) was passed from a graduated aspirator into a clear warm solution of *p*-acetamidobenzenesulphinic acid (4 g.) in aqueous ammonia (*d* 0·88, 4 c.c.), water (4 c.c.), and ethyl alcohol (6 c.c.) at a slow rate such that the temperature

was maintained at 35—40°. Towards the end of the reaction a mass of colourless needles separated. The mixture was cooled in ice and the crystalline deposit collected at the pump and air-dried at 50° (2·75 g., m. p. 207°). Recrystallisation from water gave *p*-acetamidobenzenesulphonamide (2·5 g.) in colourless needles, m. p. 219°, alone or on admixture with an authentic specimen prepared by the method of Gelmo (*J. pr. Chem.*, 1908, **77**, 371).

Action of Sodium Hypochlorite on Ammonium p-*Acetamidobenzenesulphinate.*—A 12% aqueous solution of sodium hypochlorite (7·8 c.c.) was added slowly to a solution of *p*-acetamidobenzenesulphinic acid (2·5 g.) and aqueous ammonia (*d* 0·88, 1·5 c.c.) in water (5 c.c.) at 35—40°. Neutralisation with hydrochloric acid gave *p*-acetamidobenzenesulphonamide (1·9 g.), m. p. and mixed m. p. 219°.

Action of Chlorine on Ammonium p-*Nitrobenzenesulphinate.*—Chlorine (225 c.c.) was passed slowly into a solution of *p*-nitrobenzenesulphinic acid (1·87 g.) in water (3 c.c.), aqueous ammonia (*d* 0·88, 2 c.c.), and alcohol (3 c.c.) at 35—40°. Pale yellow needles (1·02 g.) separated on cooling. Recrystallisation from water gave *p*-nitrobenzenesulphonamide in pale yellow needles, m. p. and mixed m. p. with an authentic specimen 177°, in agreement with Blanksma (*Rec. Trav. chim.*, 1901, **20**, 129).

Action of Sodium Hypochlorite on Ammonium p-*Nitrobenzenesulphinate.*—Aqueous sodium hypochlorite (9·4%, 4 c.c.) was added slowly to a solution of *p*-nitrobenzenesulphinic acid (0·93 g.) in water (2 c.c.), aqueous ammonia (*d* 0·88, 0·75 c.c.), and alcohol (3 c.c.). The solution was neutralised with hydrochloric acid and the precipitated sulphonamide (0·4 g.) crystallised from water. The *p*-nitrobenzenesulphonamide, which was obtained in pale yellow needles, m. p. and mixed m. p. 177°, was boiled with stirring under reflux with iron filings (1·5 g.) and methylated spirit (25 c.c.) containing water (0·25 c.c.) and concentrated hydrochloric acid (0·1 c.c.). After 12 hours a further portion (0·1 c.c.) of concentrated hydrochloric acid was added and boiling was continued for a further 12 hours. The mixture was filtered hot and the filtrate made alkaline with 40% aqueous sodium hydroxide. The precipitated iron hydroxide was removed by filtration with the aid of charcoal, and the filtrate, after neutralisation with hydrochloric acid, was evaporated to dryness. Extraction of the residue with absolute alcohol gave *p*-aminobenzenesulphonamide (0·2 g.) in colourless prisms, m. p. 163°, alone or on admixture with an authentic specimen.

*Action of Chlorine on Ammonium ω-Acetamido-*p-*toluenesulphinate.*—Chlorine (225 c.c.) was passed into a solution of ω-acetamido-*p*-toluenesulphinic acid (2·13 g.) in water (5 c.c.) containing ammonia (*d* 0·88, 2 c.c.) and alcohol (5 c.c.) at 35—40°. The crystalline deposit which separated overnight was collected at the pump, washed with a little water, and air-dried at 50°. Recrystallisation from alcohol gave ω-acetamido-*p*-toluenesulphonamide (1·23 g.) in colourless needles, m. p. 173°, alone or on admixture with an authentic specimen prepared from ω-acetamido-*p*-toluenesulphonyl chloride and ammonia, as described by Bergeim and Braker (*loc. cit.*) (cf. Miller, Sprague, Kissinger, and McBurney, *J. Amer. Chem. Soc.*, 1940, **62**, 2102).

Action of Chlorine on 2-Aminopyridine p-*Acetamidobenzenesulphinate.*—Chlorine (225 c.c.) was passed into a solution of *p*-acetamidobenzenesulphinic acid (2 g.) and 2-aminopyridine (2·8 g.) in water (50 c.c.) at 0° during 10 minutes. The white solid which had separated during the reaction was filtered off, washed successively with water, alcohol, and ether, and dried [0·13 g., m. p. 247° (decomp.)]. This insoluble product was regarded as acetanilide-*p*-disulphone (Found : N, 7·2. Calc. for $C_{14}H_{16}O_6N_2S_2$: N, 7·1%), previously prepared by Child and Smiles (*loc. cit.*) from *p*-acetamidobenzenesulphinic acid and potassium permanganate in glacial acetic acid solution. The filtrate was left for 2 days at room temperature, during which time crude 2-(*p*-acetamidobenzenesulphonamido)pyridine separated; crystallisation of this from 70% alcohol gave 0·52 g., m. p. 225°, alone or on admixture with an authentic specimen prepared from *p*-acetamidobenzenesulphonyl chloride and 2-aminopyridine (Crossley, Northey, and Hultquist, *J. Amer. Chem. Soc.*, 1940, **62**, 372). Hydrolysis by boiling under reflux for 2 hours with 2N-sodium hydroxide followed by addition of hydrochloric acid to pH 6 precipitated 2-(*p*-aminobenzenesulphonamido)pyridine, which separated from alcohol in prisms, m. p. 190°, alone or on admixture with an authentic specimen. When the chlorination was carried out at 35—40° the yield of the disulphone was increased at the expense of the sulphonamide. The reaction did not take place when water was replaced by dioxan or alcohol as solvent. Part of the excess of 2-aminopyridine could be replaced by sodium carbonate.

Action of Chlorine on 2-Aminopyridine p-*Nitrobenzenesulphinate.*—Chlorine (225 c.c.) was passed into a solution of *p*-nitrobenzenesulphinic acid (1·87 g.), 2-aminopyridine (1·88 g.), and anhydrous sodium carbonate (1·06 g.) in water (50 c.c.) with shaking and ice-cooling during 10 minutes. After several days the crystalline deposit was collected; recrystallisation from 50% acetic acid gave 2-(*p*-nitrobenzenesulphonamido)pyridine (0·24 g.) in pale yellow needles, m. p. 180°, alone or an admixture with an authentic specimen prepared from *p*-nitrobenzenesulphonyl chloride and 2-aminopyridine (Ewins and Phillips, B.P. 512,145; cf. Barber, B.P. 550,446).

The action of chlorine, in similar manner, on the salts of *p*-acetamidobenzenesulphinic acid and of *p*-nitrobenzenesulphinic acid with 2-aminothiazole, 2-aminopyrimidine, and 2-amino-4 : 6-dimethylpyrimidine, did not yield the corresponding sulphonamides. In most cases the only products isolated were acetanilide-*p*-disulphone or nitrobenzene-*p*-disulphone and sulphonic acids.

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37. *Synthetic Oestrogens of the Triphenylethylene Series.*

By P. R. Carter and D. H. Hey.

Several new mono-, di- and tri-*p*-alkoxytriphenylbromoethylenes have been prepared as synthetic oestrogens by bromination of the corresponding diphenylbenzylcarbinols. The latter were obtained by means of Grignard reactions between (*a*) a benzophenone and a benzylmagnesium halide, (*b*) a phenylacetic ester and a phenylmagnesium halide, or (*c*) a deoxybenzoin and a phenylmagnesium halide. Some of the bromoethylenes exist in geometrically isomeric forms. An improved preparation of *p*-hydroxyphenylacetic acid is described.

The oestrogenic activity of triphenylethylene was first reported almost simultaneously and independently by Robson and Schönberg (*Nature*, 1937, **140**, 196) and by Dodds, Fitzgerald, and Lawson (*Nature*, 1937, **140**, 772). It was subsequently found that non-nuclear halogen substitution of triphenylethylene enhances the oestrogenic activity, and according to Robson, Schönberg, and Fahim (*Nature*, 1938, **142**, 292) chlorotriphenylethylene is some twenty times more active than the unsubstituted triphenylethylene. More recently Segaloff (*Endocrinology*, 1944, **34**, 335) has claimed that chlorotriphenylethylene is one hundred times more active than triphenylethylene. On the other hand nuclear halogen substitution at the *para* positions either destroys the oestrogenic activity completely or reduces it to very small proportions (Schönberg, Robson, Tadros, and Fahim, *J.*, 1940, 1327). Alkyl groups attached to the ethylenic carbon atom increase the oestrogenic activity in a similar manner to a halogen atom, but not to such a large extent (Davies and Elson, B.P. 549,353); the cyano-group is much less effective (Badger, Elson, Haddow, Hewett, and Robinson, *Proc. Roy. Soc.*, 1942, *B*, **130**, 255). Probably the most interesting members in this series of synthetic oestrogens are those containing one or more alkoxy-groups at the *para* position in the aromatic nuclei, and among these 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene (B.P. 549,200, 559,374) and 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene or DBE (Robson and Schönberg, *Nature*, 1942, **150**, 22; Schönberg and Tadros, B.P. 563,811) have attracted most attention. The importance of the alkoxy-derivatives probably arises from the fact that one or more free phenolic groups are formed during the metabolic processes (Stroud, *Nature*, 1939, **144**, 245; 1940, **146**, 166). This is in keeping with the prolonged action which is characteristic of oestrogens of this type and differentiates them from synthetic oestrogens of the stilboestrol type (cf. Robson and Ansari, *J. Pharm. Exp. Ther.*, 1943, **79**, 340; Greene, *Brit. Med. J.*, 1946, i, 9; Way, *ibid.*, p. 10). With regard to the effect of alkoxy-groups on oestrogenic activity in the triphenylethylene series, Davies and Basford (B.P. 549,200 and 559,374) have claimed that 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene is more active than 2-bromo-2-phenyl-1 : 1-di-*p*-anisylethylene, which, according to Schönberg, Robson, Tadros, and Fahim (*loc. cit.*), has the same activity as 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene. Further, Basford (B.P. 561,508) states that chlorotri-*p*-anisylethylene is ten times more active than chlorotriphenylethylene. This seems to indicate that in the triphenylethylene series, as with synthetic oestrogens of the stilboestrol type, the maximum activity requires substitution by hydroxy- or alkoxy-groups at the *para* positions in at least two benzene nuclei attached to different ethylenic carbon atoms. This indication is supported by the observation of Dodds, Golberg, Grünfeld, Lawson, Saffer, and Robinson (*Proc. Roy. Soc.*, 1944, *B*, **132**, 83) that 4 : 4′-dihydroxy-β-phenyl-α-ethylstilbene is not less than one-twelfth as active as stilboestrol, and would appear to be the most active derivative of triphenylethylene so far reported.

In order to obtain further information concerning the relationship between chemical constitution and intensity and duration of oestrogenic activity in the triphenylethylene series a number of new mono-, di-, and tri-*p*-alkoxy-bromotriphenylethylenes and one substituted chlorotriphenylethylene have been prepared. Although the corresponding free phenols might in general possess greater activity than the alkyl ethers, their effect is likely to be of shorter duration owing to rapid excretion and decomposition in the body. In this series of synthetic oestrogens duration of activity is of greater importance than high intrinsic activity provided the compound is sufficiently non-toxic for therapeutic doses to be administered with safety and without undesirable side-effects such as nausea and vomiting.

The bromo-*p*-alkoxytriphenylethylenes were prepared by the action of bromine on the corresponding substituted diphenylbenzylcarbinols in glacial acetic acid solution at room temperature. In one instance a chlorotriphenylethylene was prepared by the action of chlorine under similar conditions. This procedure is preferred to the bromination of the substituted triphenylethylenes formed from the carbinols by dehydration, since it eliminates one stage and the solid carbinols are more convenient for purification when working with small quantities.

The substituted diphenylbenzylcarbinols were prepared by the following three methods (R, R′, and R″ = *p*-O-Alkyl or H).

Method *A*. Reaction of a *p*-alkoxybenzophenone with a benzylmagnesium halide :

$$R{\cdot}C_6H_4{\cdot}CO{\cdot}C_6H_4{\cdot}R + Ph{\cdot}CH_2{\cdot}Mg{\cdot}Hal \longrightarrow (R{\cdot}C_6H_4)_2C(OH){\cdot}CH_2Ph$$

Method *B*. Reaction of a *p*-alkoxyphenylacetic ester with a *p*-alkoxyphenylmagnesium halide :

$$R{\cdot}C_6H_4{\cdot}CH_2{\cdot}CO_2Et + 2R'{\cdot}C_6H_4{\cdot}Mg{\cdot}Hal \longrightarrow (R'{\cdot}C_6H_4)_2C(OH){\cdot}CH_2{\cdot}C_6H_4{\cdot}R$$

Method *C*. Reaction of a *p*-alkoxy-deoxybenzoin with a *p*-alkoxyphenylmagnesium halide :

$$R{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}C_6H_4{\cdot}R' + R''{\cdot}C_6H_4{\cdot}Mg{\cdot}Hal \longrightarrow \begin{matrix} R{\cdot}C_6H_4 \\ R''{\cdot}C_6H_4 \end{matrix}\!\!>\!C(OH){\cdot}CH_2{\cdot}C_6H_4{\cdot}R'$$

Method *C* provides two routes to the same carbinol by interchanging R and R″. In one case method *B* gave a substituted triphenylethylene, namely 2-*p*-ethoxyphenyl-1 : 1-di-*p*-*n*-propoxyphenylethylene, in place of the carbinol, but on repeating the Grignard reaction under milder conditions the expected carbinol was obtained in the normal manner. Method *A* had been applied to *para*-substituted benzophenones by Busignies (*Compt. rend.*, 1910, **151**, 516), Ley and Kirchner (*Z. anorg. Chem.*, 1928, **173**, 395), and Koelsch (*J. Amer. Chem. Soc.*, 1932, **54**, 2487), and after the completion of this work Basford reported further examples (B.P. 566,415). This method was also used by Schönberg and Tadros (*J.*, 1943, 394; B.P. 563,810). Attempts to extend the applicability of this reaction to the preparation of tri-*p*-alkoxy-diphenylbenzylcarbinols by the utilisation of a Grignard reagent from a *p*-alkoxybenzyl halide were unsuccessful. Method *B* has also been employed with unsubstituted ethyl phenylacetate by Koelsch (*loc. cit.*), who claimed that the method was applicable only to the preparation of di-substituted compounds. It has now been extended to include the preparation of tri-*p*-alkoxy-derivatives by the use of *p*-alkoxyphenylacetic esters. Method *C* has been used by Dodds, Golberg, Lawson, and Robinson (*Proc. Roy. Soc.*, 1939, *B*, **127**, 161) and by Davies (B.P. 549,200) and more recently by Basford (B.P. 566,415, 567,807). In all three methods it was found desirable to use excess of the Grignard reagent, two molecular proportions being used in the reactions with ketones (*A* and *C*), and three molecular proportions in the reactions with esters (*B*).

The *p*-alkoxyphenylacetic esters for use in Method *B* were prepared by alkylation of *p*-hydroxyphenylacetic acid, which has now been obtained in almost theoretical yield by diazotisation of *p*-aminophenylacetic acid. This represents a considerable improvement on the methods of Salkowski (*Ber.*, 1879, **12**, 1438) and Pschorr, Wolfes, and Buckow (*Ber.*, 1900, **33**, 171), and avoids the necessity of having recourse to the more involved methods of preparation due to Cain, Simonsen, and Smith (*J.*, 1913, **103**, 1036) and Kindler, Metzendorf, and Dschi-yin-Kwok (*Ber.*, 1943, **76**, 308).

Certain of the above bromotriphenylethylenes, namely those which contain two different *p*-alkoxyphenyl groups attached to the same carbon atom, should exist in geometrically isomeric forms, but only in the case of 2-bromo-1-phenyl-1-*p*-anisyl-2-*p*-ethoxyphenylethylene was it possible to isolate both *cis*- and *trans*-forms. Inconclusive evidence was obtained of the existence of 2-bromo-1 : 2-diphenyl-1-*p*-ethoxyphenylethylene in geometrically isomeric forms, but the results were complicated by the existence of one of the forms in polymorphic modifications. 2-Bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene also appears to exist in two polymorphic forms, and 2-bromo-2-phenyl-1-*p*-ethoxyphenyl-1-*p*-*n*-propoxyphenylethylene was probably obtained as a mixture of *cis*- and *trans*-isomerides. Doubtless both isomerides are formed together in most cases, but only the more insoluble or the more abundant form was obtained in the method of isolation which was not quantitative. Similar observations were recorded by Dodds, Golberg, Lawson, and Robinson (*loc. cit.*) in the case of 1-phenyl-1 : 2-di-*p*-anisylethylene. Koelsch (*loc. cit.*) had previously reported the isolation of both *cis*- and *trans*-forms of 2-bromo-1 : 2-diphenyl-1-*p*-chlorophenylethylene, and by converting them into indones had assigned probable constitutions to the two forms, although, as stated, the proof is not rigid.

At the time of the commencement of this work the only bromoalkoxytriphenylethylenes established were 2-bromo-1 : 2-diphenyl-1-*p*-anisylethylene and 2-bromo-2-phenyl-1 : 1-di-*p*-anisylethylene (Koelsch, *loc. cit.*), 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene (DBE) (Tadros and Schönberg, *loc. cit.*), and 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene (B.P. 549,200). During the course of this investigation preparations of 2-bromo-2-phenyl-1-*p*-anisyl-2-*p*-ethoxyphenylethylene, 2-bromo-1-*p*-ethoxyphenyl-1 : 2-di-*p*-anisylethylene (B.P. 566,415), and 2-bromo-1-phenyl-1 : 2-di-*p*-ethoxyphenylethylene (B.P. 567,807) were reported. Later preparations of

2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene and 2-bromo-1 : 1 : 2-tri-*p*-anisylethylene have also been reported in B.P. 567,807 and B.P. 559,374 respectively.

Tests carried out by Dr. J. M. Robson showed that many of the new compounds described in this paper possessed oestrogenic activity with a duration of action comparable with that previously associated with 2-bromo-2-phenyl-1 : 1-di-*p*-ethoxyphenylethylene. Full details will be published elsewhere.

Experimental.

Preparation of Ketones.—*4 : 4′-Diethoxybenzophenone.* Ethyl iodide (100 g.) was added slowly to a boiling solution of 4 : 4′-dihydroxybenzophenone (66 g.), prepared as described by Baeyer and Burkhardt (*Annalen*, 1880, **202**, 126), and sodium (13·8 g.) in absolute alcohol (600 c.c.). Boiling under reflux was continued for 1 hour, after which a solution of sodium (6·9 g.) in alcohol (150 c.c.) and ethyl iodide (50 g.) were added in turn. The mixture was boiled under reflux for a further 3 hours until neutral. The alcohol was removed on the steam-bath and water was added to the residue. The solid 4 : 4′-diethoxybenzophenone (76·8 g.) was collected at the pump, washed with water, and dried at 60°. It had m. p. 131° in agreement with Staedel and Beck (*Annalen*, 1878, **194**, 330).

Phenyl p-ethoxybenzyl ketone. *p*-Ethoxyphenylacetic acid was prepared by ethylation of crude *p*-hydroxyphenylacetic acid, obtained from *p*-aminophenylacetic acid (20·2 g.) as described below. The resultant mixture of *p*-ethoxyphenylacetic acid and its ethyl ester was boiled under reflux for 2 hours with 2N-sodium hydroxide (200 c.c.), and acidification of the cooled solution gave crystalline *p*-ethoxyphenylacetic acid (21·2 g.), which was collected, washed with water, and dried (m. p. 84°). Crystallisation from dilute alcohol raised the m. p. to 88° as recorded by Salkowski (*Ber.*, 1879, **12**, 1440), who gave no analytical figures for the compound. A mixture of *p*-ethoxyphenylacetic acid (21·2 g.) and phosphorus trichloride (8·3 g.) was heated for 2 hours at 100°. Dry benzene (100 c.c.) was added to the warm acid chloride, and the solution was decanted and added to an ice-cold mixture of dry benzene (50 c.c.) and freshly ground aluminium chloride (19 g.) with mechanical stirring. The mixture was stirred over-night with ice-cooling and then for 8 hours with the addition of ice and concentrated hydrochloric acid. The product was extracted with ether–benzene, washed successively with aqueous sodium hydroxide and water, and dried (Na_2SO_4). After removal of the solvent on the steam-bath the residue was purified by chromatographic adsorption on alumina from benzene solution, and finally crystallised from benzene–alcohol. Phenyl *p*-ethoxybenzyl ketone (3·8 g.) was obtained in colourless prisms, m. p. 110°, in agreement with Tiffeneau, Orékhov, and Roger (*Bull. Soc. chim.*, 1931, **49**, 1763), who obtained the ketone by the deamination of 2-hydroxy-2-phenyl-2-*p*-ethoxyphenylethylamine.

p-Ethoxyphenyl benzyl ketone, m. p. 103°, was prepared in 45% yield from phenylacetic acid, phosphorus trichloride, aluminium chloride, and phenetole in carbon disulphide solution by the method of Tiffeneau, Orékhov, and Roger (*loc. cit.*). When stannic chloride was used in place of aluminium chloride, as recommended by Wilds and Biggerstaff (*J. Amer. Chem. Soc.*, 1945, **67**, 789), the yield was increased to 71%.

Phenyl p-n-*propoxybenzyl ketone* was prepared from *p*-*n*-propoxyphenylacetic acid (15·3 g.), phosphorus trichloride (5·5 g.), aluminium chloride (12 g.), and benzene (150 c.c.) as described above for the preparation of phenyl *p*-ethoxybenzyl ketone. It was obtained in colourless plates (3·5 g.), m. p. 92° (Found: C, 80·3; H, 7·2. $C_{17}H_{18}O_2$ requires C, 80·3; H, 7·1%). p-n-*Propoxyphenylacetic acid* was prepared from ethyl *p*-*n*-propoxyphenylacetate (15 g.), obtained as described below, by hydrolysis with boiling 2N-sodium hydroxide (50 c.c.) for 2 hours. After filtration with charcoal, the filtrate was acidified with concentrated hydrochloric acid and extracted with ether. The residue, obtained on removal of the ether, was crystallised from aqueous alcohol and gave the acid (11 g.) in colourless plates, m. p. 91° (Found: C, 68·7; H, 7·4. $C_{11}H_{14}O_3$ requires C, 68·1; H, 7·2%).

Preparation of Esters.—*Ethyl p-ethoxyphenylacetate.* A solution of *p*-aminophenylacetic acid (30·2 g.), prepared as described by Robertson (*Org. Synth.*, Coll. Vol. I, 52), in a mixture of concentrated sulphuric acid (40 c.c.) and water (320 c.c.) was cooled in a freezing mixture and a solution of sodium nitrite (14 g.) in water (40 c.c.) was added dropwise with stirring during 10 minutes at 2—3°. After a further 10 minutes the clear pale yellow solution of the diazonium salt, kept at 0°, was added during ½ hour in 10—20 c.c. portions to a refluxing mixture of concentrated sulphuric acid (40 c.c.) and water (320 c.c.). The resulting clear pale yellow solution containing no tar was cooled, saturated with sodium sulphate, and extracted with ether. Removal of the ether from the dried (Na_2SO_4) extract left the crude hydroxy-acid (30·4 g.) as a brownish solid, m. p. *ca.* 140°. Crystallisation from water gave pure *p*-hydroxyphenylacetic acid, m. p. 148°, in agreement with Salkowski (*loc. cit.*), who prepared it by a similar procedure but gave no yield, and with Pschorr, Wolfes, and Buckow (*loc. cit.*), who claimed only a 50% yield. Ethyl iodide (66 g.) was added to a boiling solution of the crude *p*-hydroxyphenylacetic acid (30·4 g.) in absolute alcohol (400 c.c.) containing sodium (9·2 g.), and after 2 hours' boiling under reflux a solution of sodium (4·6 g.) in absolute alcohol (100 c.c.), followed by a further quantity of ethyl iodide (33 g.), was added. The mixture was boiled for a further 3 hours until neutral, after which the bulk of the alcohol was removed on the steam-bath. Excess of ice-cold dilute hydrochloric acid was added to the residue, which was then extracted with ether. The extract was washed successively with aqueous sodium hydrogen sulphite and water, and after drying (Na_2SO_4) the ether and remainder of the alcohol were distilled off on the water-bath, finally under reduced pressure, leaving a mixture of solid *p*-ethoxyphenylacetic acid containing a little ethyl *p*-ethoxyphenylacetate. This crude mixture was boiled under reflux for 3 hours with absolute ethyl alcohol (200 c.c.) containing concentrated sulphuric acid (8 c.c.). The cold mixture was diluted with water and extracted with ether, and the extract was washed successively with aqueous sodium carbonate and water and dried (Na_2SO_4). The ether and alcohol were removed on the steam-bath, and distillation of the residue under reduced pressure gave *ethyl* p-*ethoxyphenylacetate* (33·4 g.) as a very pale yellow oil, b. p. 130°/3 mm., 148°/7 mm. (Found: C, 69·2; H, 7·8. $C_{12}H_{16}O_3$ requires C, 69·2; H, 7·7%).

Ethyl p-n-*propoxyphenylacetate.* Crude *p*-hydroxyphenylacetic acid (30·4 g.), prepared as described above, was boiled under reflux for 2 hours with absolute ethyl alcohol (150 c.c.) containing concentrated sulphuric acid (6 c.c.). After removal of the bulk of the alcohol on the steam-bath the cooled residue was treated with water and extracted with ether. The extract was washed with aqueous sodium carbonate and with water, and dried (Na_2SO_4). Distillation of the ether and removal of the alcohol under reduced pressure gave crude ethyl *p*-hydroxyphenylacetate (31·25 g.), which was added to a solution of sodium (3·45 g.) in absolute alcohol (100 c.c.). *n*-Propyl bromide (18·5 g.) was added to the boiling solution under reflux, and after 2 hours a further addition of sodium (1·75 g.) in absolute alcohol (50 c.c.) followed by *n*-propyl bromide (10 g.) was made. After a further 2 hours' boiling under reflux the bulk of the alcohol was removed on the steam-bath and ice–water was added to the cold residue, which was extracted with ether. After the extract had been washed with aqueous sodium hydroxide and with water, and dried (Na_2SO_4), the ether was removed; distillation of the residue under reduced pressure gave *ethyl* p-n-*propoxyphenylacetate* (26 g.) as a pale yellow oil, b. p. 160°/6 mm. (Found: C, 70·25; H, 7·8. $C_{13}H_{18}O_3$ requires C, 70·3; H, 8·1%).

Methyl p-*anisylacetate.* To a boiling solution of crude *p*-hydroxyphenylacetic acid, prepared as described above from *p*-aminophenylacetic acid (30·2 g.), dissolved in a solution of sodium (9·2 g.) in absolute alcohol (400 c.c.), was added methyl iodide (60 g.). Boiling under reflux was continued for 2 hours, after which a further solution of sodium (4·6 g.) in absolute alcohol (100 c.c.) followed by methyl iodide (30 g.) were added. After a further two hours' boiling under reflux the bulk of the alcohol was removed on the steam-bath and the cooled residue treated with ice–water and dilute acid and extracted with ether. The extract was washed successively with aqueous sodium hydrogen sulphite, water, 2N-sodium hydroxide, and water, and finally dried ($NaSO_4$). Removal of the ether and distillation of the residue under reduced pressure gave methyl *p*-anisylacetate (14·7 g.) as a very pale yellow oil, b. p. 141—142°/16 mm. Pschorr, Wolfes, and Buckow (*loc. cit.*) give b. p. 155—157°/23 mm. for the ester prepared from *p*-hydroxyphenylacetic acid, methyl iodide, and potassium hydroxide in methyl alcohol at 100°.

Ethyl p-*anisylacetate.* The sodium hydroxide washings from the preparation of methyl *p*-anisylacetate were acidified and extracted with ether. After the extract had been washed with aqueous sodium hydrogen sulphite and with water and dried (Na_2SO_4), the ether was removed and the residual *p*-anisylacetic acid was boiled under reflux for 3 hours with ethyl alcohol (100 c.c.) containing concentrated sulphuric acid (4 c.c.). After removal of the bulk of the alcohol on the steam-bath the cooled residue was treated with water and extracted with ether. The extract was washed with aqueous sodium hydroxide and with water and dried (Na_2SO_4). Removal of the ether, followed by distillation under reduced pressure, gave ethyl *p*-anisylacetate (6·5 g.) as a very pale yellow oil, b. p. 138—140°/7 mm. Cain, Simonsen, and Smith (*loc. cit.*) give b. p. 138—140°/7 mm. for the ester prepared by oxidation of *p*-anisylpyruvic acid followed by esterification.

Preparation of p-*Alkoxyphenyl Bromides.*—*p*-Bromophenetole was prepared by the bromination of phenetole in carbon disulphide, as described by Michaelis (*Ber.*, 1894, **27**, 258), whereas *p*-bromoanisole was prepared in similar manner but in carbon tetrachloride solution (cf. Michaelis and Weitz, *Ber.*, 1887, **20**, 49). In both reactions yields of 90% were obtained. Phenyl *n*-propyl ether was prepared by the addition of *n*-propyl bromide (123 g.) to a boiling solution of phenol (94 g.) in absolute ethyl alcohol (1000 c.c.) containing sodium (23 g.). After 2 hours a further quantity of sodium (11·5 g.) in alcohol (500 c.c.) was added, followed by more *n*-propyl bromide (62 g.). After two hours' boiling under reflux the alcohol was removed and the residue treated with water and extracted with ether. Removal of the ether from the dried extract left phenyl *n*-propyl ether, which was collected as a colourless oil (100 g.) at 190° (cf. Cahours, *Bull. Soc. chim.*, 1874, **21**, 78). Bromine (118 g.) was added dropwise to a stirred solution of the ether (100 g.) in carbon disulphide (300 c.c.) at 0°. The resulting pale yellow solution was washed with water and with aqueous sodium thiosulphate. After removal of the solvent the *p*-bromophenyl *n*-propyl ether (152 g.) was collected as a pale yellow oil at 128°/24 mm. (Found: C, 50·6; H, 5·5. Calc. for $C_9H_{11}OBr$: C, 50·2; H, 5·2%). Bradfield and Jones (*J.*, 1931, 2903) reported this compound but gave no experimental details.

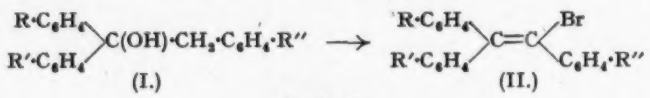
Preparation of Carbinols. General Methods.—Method A. The Grignard reagent, prepared from freshly distilled benzyl chloride (0·5 mol.) and magnesium (0·5 mol.) in dry ether (400 c.c.), was treated, with ice-cooling and stirring, with the benzophenone (0·25 mol.). After boiling under reflux for 2 hours and standing over-night, the mixture was added to a mixture of crushed ice (2 kg.) and ammonium chloride (200 g.). The carbinol which separated was filtered off, washed with water and a little ether, and dried and/or extracted with ether and the ethereal layer was separated, dried (Na_2SO_4), and evaporated. The carbinols were crystallised from light petroleum (b. p. 60—80°) and were usually obtained in the form of colourless needles in good yield.

Method B. The Grignard reagent, prepared from magnesium (1·0 mol.), freshly distilled bromo-compound (1·0 mol.), and ether (625 c.c.), was treated, with ice-cooling and stirring, with a solution of the phenylacetic ester (0·33 mol.) in ether (275 c.c.) added dropwise. After being heated under reflux for 2 hours and left over-night the mixture was poured on crushed ice (2 kg.) and ammonium chloride (250 g.), and the carbinol was isolated in yields varying from 40 to 70% (calculated on ester) as described above under Method *A*. In one instance this procedure led to the ethylene and not the carbinol, but repetition of the reaction without heating under reflux gave the carbinol in the normal manner (see later).

Method C. The Grignard reagent, prepared from magnesium (0·5 mol.), the bromo-compound (0·5 mol.), and ether (500 c.c.), was treated, with ice-cooling and stirring, with a solution of the deoxybenzoin (0·25 mol.) in ether (500 c.c.) added dropwise. After boiling under reflux for two hours, the mixture was cooled and poured on a mixture of crushed ice and ammonium chloride. The carbinol was extracted with ether or benzene. After the extract had been dried and the solvent removed, the residual carbinol crystallised from light petroleum (b. p. 60—80°). Yields varied from 40 to 60% calculated on the deoxybenzoin.

Preparation of Bromoethylenes. General Method.—A solution of bromine (1·6 g., 0·01 mol.) in glacial

Carbinols and Bromoethylenes (R, R′, and R″ = *p*-*O*-Alkyl or H).



						Analysis. Found, %.		Calc, %.				Analysis. Found, %.		Calc, %.	
R.	R′.	R″.	Carbinol (I).	M. p.	Prep.	C.	H.	C.	H.	Bromoethylene (II).	M. p.	C.	H.	C.	H.
H	H	MeO	$C_{21}H_{20}O_2$	142°	*B*	82·5	6·4	82·9	6·6	$C_{21}H_{17}OBr$	130°	68·6	4·8	69·0	4·7
H	EtO	H	$C_{23}H_{22}O_2$ ‡ §	86—87	*C*	82·85	7·0	83·0	6·9	$C_{23}H_{19}OBr$ ‡	83—84	69·4	5·1	69·7	5·0
										$C_{23}H_{19}OBr$	92	69·2	5·0	69·7	5·0
										$C_{23}H_{19}OBr$	111	69·3	5·1	69·7	5·0
H	H	EtO	$C_{23}H_{22}O_2$	97·5	*B*	82·7	6·8	83·0	6·9	$C_{23}H_{19}OBr$	95	69·8	5·0	69·7	5·0
MeO	MeO	MeO	$C_{23}H_{24}O_4$ †	129	*B*	75·9	6·5	75·8	6·5	$C_{23}H_{21}O_3Br$ †	120	64·9	4·9	64·9	5·1
H	MeO	EtO	$C_{23}H_{24}O_3$ ‖	89	*C*	79·3	6·9	79·3	6·9	$C_{23}H_{21}O_3Br$	106	67·6	5·0	67·5	5·1
										$C_{23}H_{21}O_3Br$	153	67·9	5·4	67·5	5·1
H	*n*-PrO	H	$C_{25}H_{26}O_2$ §	84	*C*	82·8	6·9	83·1	7·2	$C_{23}H_{21}OBr$	118	69·9	5·5	70·2	5·3
H	H	*n*-PrO	$C_{25}H_{26}O_2$	71	*B*	83·0	7·4	83·1	7·2	$C_{25}H_{21}OBr$	92	70·3	5·3	70·2	5·3
MeO	MeO	EtO	$C_{26}H_{28}O_4$	116	*B*	76·1	7·0	76·2	6·9	$C_{24}H_{23}O_3Br$	76	65·6	5·5	65·6	5·2
EtO	EtO	H	$C_{24}H_{24}O_3$ *	124	*A*, *B*	—	—	—	—	$C_{24}H_{23}O_3Br$ *	97	—	—	—	—
										$C_{24}H_{23}O_3Br$	87	—	—	—	—
H	MeO	*n*-PrO	$C_{26}H_{28}O_3$ **	107	*C*	79·5	7·05	79·5	7·2	$C_{26}H_{27}O_3Br$	85	68·2	5·4	68·1	5·4
EtO	EtO	MeO	$C_{26}H_{28}O_4$	107	*B*	76·3	7·2	76·5	7·1	$C_{25}H_{25}O_3Br$	81	65·7	5·4	66·2	5·5
EtO	*n*-PrO	H	$C_{27}H_{30}O_3$ ¶	105	*C*	80·1	6·9	79·8	7·45	$C_{25}H_{25}O_3Br$	*ca.* 70	66·2	5·4	68·6	5·7
H	*n*-PrO	EtO	$C_{27}H_{30}O_3$ ‖	86	*C*	79·5	7·3	79·8	7·45	$C_{25}H_{25}O_2Br$	71	68·1	5·6	68·6	5·7
EtO	EtO	EtO	$C_{28}H_{32}O_4$	116	*B*	77·1	7·4	76·9	7·4	$C_{26}H_{27}O_2Br$	81—82	66·6	6·0	66·8	5·8
n-PrO	*n*-PrO	EtO	$C_{28}H_{34}O_4$	85	*B*	76·8	7·8	77·4	7·8	$C_{28}H_{31}O_3Br$	86	68·2	6·3	67·9	6·3

* Previously prepared by Tadros and Schönberg (*J.*, 1943, 394) by Method *A*.
† Previously prepared by Davies (B.P. 549,200).
‡ Prepared by Dr. W. H. Hook.
§ Prepared from deoxybenzoin.
‖ Prepared from phenyl *p*-ethoxybenzyl ketone.
¶ Prepared from *p*-ethoxyphenyl benzyl ketone.
** Prepared from phenyl *p*-*n*-propoxybenzyl ketone.

acetic acid (16 c.c.) was added to a solution or suspension of the carbinol (0·01 mol.) in the same solvent (30 c.c.). The temperature was maintained below 20°. After two hours' stirring at room temperature the bulk of the acetic acid was removed under reduced pressure on the water-bath, and the residual bromoethylene was filtered off and recrystallised from absolute alcohol or light petroleum (b. p. 80—100°). Alternatively, the bromo-compound was thrown out of solution, usually as an oil, by the addition of water to the solution in glacial acetic acid. Many carbinols and bromoethylenes were purified by chromatographic adsorption on activated alumina, from solution in either light petroleum (b. p. 80—100°) or a mixture of that solvent with 10% v/v of benzene, followed by elution with the same solvent. In this manner it was frequently found possible to isolate the products in pure crystalline form from a crude product in the form of a brown viscous oil. The pure bromoethylenes were usually obtained as very pale yellow or almost colourless needles or prisms.

The carbinols and bromoethylenes prepared in this way are listed in the Table.

2-Chloro-1 : 1-*di*-p-*anisyl*-2-p-*ethoxyphenylethylene*.—Chlorine (225 c.c.) was delivered slowly from a graduated aspirator into a solution of di-*p*-methoxyphenyl-*p*-ethoxybenzylcarbinol (3·78 g.) in glacial acetic acid (30 c.c.) at room temperature. After several hours the product was precipitated as an oil by dilution with water. The oil was extracted with light petroleum (b. p. 80—100°), dried, and purified by chromatographic adsorption on alumina. *2-Chloro*-1 : 1-*di*-p-*anisyl*-2-p-*ethoxyphenylethylene* (1·7 g.) crystallised from absolute ethyl alcohol in colourless prisms, m. p. 82° (Found: C, 72·4; H, 5·7. $C_{24}H_{23}O_3Cl$ requires C, 73·0; H, 5·8%).

2-p-*Ethoxyphenyl*-1 : 1-*di*-n-*propoxyphenylethylene*.—A solution of ethyl *p*-ethoxyphenylacetate (7 g.) in dry ether (50 c.c.) was added to the Grignard reagent prepared in the usual manner from *p*-bromo-*n*-propoxybenzene (21·5 g.) and magnesium (2·43 g.) in dry ether (125 c.c.) with ice-cooling and stirring. The mixture was boiled under reflux for 2 hours, cooled, poured on ice and ammonium chloride, and extracted with ether. Evaporation of the dried extract left an oily residue which was purified by chromatographic adsorption on alumina from light petroleum (b. p. 80—100°). Crystallisation from light petroleum (b. p. 40—60°) gave 2-p-*ethoxyphenyl*-1 : 1-*di*-n-*propoxyphenylethylene* in colourless needles, m. p. 76° (Found: C, 81·0; H, 7·5. $C_{28}H_{32}O_3$ requires C, 80·8; H, 7·7%). When the above preparation was repeated without boiling under reflux *di*-p-n-*propoxyphenyl*-p-*ethoxybenzylcarbinol*, m. p. 85° (see Table), was isolated in the normal manner. In this instance the bromoethylene was prepared by the bromination of the ethylene, and not the carbinol, using the same general procedure in glacial acetic acid solution.

Isomeric and Polymorphic Forms.—*2-Bromo*-1 : 2-*diphenyl*-1-p-*ethoxyphenylethylene*. (By Dr. W. H. Hook.) When prepared from the carbinol by the general method the bromoethylene separated from the acetic acid solution on standing over-night in transparent plates, m. p. 91—92°, which on recrystallisation from ethyl alcohol gave colourless prisms, m. p. 83—84°. After fusion and slow cooling the melting-point was raised to 91—92° again. The two forms melting at 91—92° and 83—84° are regarded as polymorphic modifications. On irradiation in solution in ethyl alcohol with ultra-violet light for 3 days, followed by slow evaporation, colourless plates, m. p. 111°, were obtained. All three forms gave correct analytical figures for $C_{22}H_{19}OBr$ (see Table). The preparation of a bromination product of 1 : 2-diphenyl-1-*p*-ethoxyphenylethylene has been reported by Busignies (*loc. cit.*), who gave m. p. 73°. This product may have been a mixture of isomeric or polymorphic forms, although it is significant that the 1 : 2-diphenyl-1-*p*-ethoxyphenylethylene from which it was obtained had m. p. 93°, whereas Ley and Kirchner (*loc. cit.*) gave m. p. 76° for this compound.

2-Bromo-1-*phenyl*-1-p-*anisyl*-2-p-*ethoxyphenylethylene*.—When prepared from the carbinol by the general method and isolated immediately by dilution with water and recrystallisation from absolute ethyl alcohol the bromoethylene was obtained in colourless needles m. p. 106°. In another preparation the brominated carbinol was allowed to stand for 12 weeks in the glacial acetic acid solution in a corked flask. During this period the bromoethylene separated slowly in long colourless needles, which after recrystallisation from absolute ethyl alcohol melted at 153°. Both forms gave correct analytical figures for $C_{23}H_{21}O_2Br$ (see Table).

2-Bromo-2-phenyl-1 : 1-*di*-p-*ethoxyphenylethylene*.—This compound separates from dilute solution in light petroleum (b. p. 80—100°) in very pale yellow prisms, m. p. 97°, but on rapid crystallisation from concentrated solutions long colourless needles, m. p. 87°, are obtained.

2-Bromo-2-phenyl-1-p-*ethoxyphenyl*-1-p-n-*propoxyphenylethylene*.—This compound (m. p. *ca.* 70°) could not be further purified to give a product with a sharp melting point, and is probably a mixture of *cis*- and *trans*-isomerides.

The authors' thanks are accorded to Dr. W. H. Hook for the preparation of 2-bromo-1 : 2-diphenyl-1-*p*-ethoxyphenylethylene and the examination of its properties, and to Dr. J. M. Robson for carrying out the physiological tests.

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38. *The Conversion of Sucrose into Furan Compounds. Part IV. Some Aminotetrahydrofuran Derivatives.*

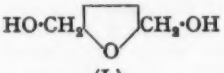
By F. H. Newth and L. F. Wiggins.

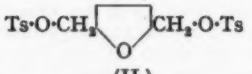
2 : 5-Bishydroxymethyltetrahydrofuran has been converted into a crystalline *di*-p-*toluenesulphonate* and also into 2 : 5-*bischloromethyltetrahydrofuran*. By means of methyl alcoholic ammonia, both of these compounds have been transformed into a secondary amine, herein

shown to be 8-*oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane*. The preparation of 2 : 5-*bis*(*diethylaminomethyl*)*tetrahydrofuran* is also described.

THE reduction product of 5-hydroxymethylfurfuraldehyde, 2 : 5-bishydroxymethyltetrahydrofuran (I) obtained by Haworth, Jones, and Wiggins, (*J.*, 1945, 1), is a convenient intermediate for the preparation of various 2 : 5-disubstituted derivatives of tetrahydrofuran. Thus, by treatment with *p*-toluenesulphonyl chloride in pyridine, it was smoothly converted into the crystalline 2 : 5-*bishydroxymethyltetrahydrofuran di*-p-*toluenesulphonate* (II). Furthermore, (I) was readily chlorinated by means of thionyl chloride to give 2 : 5-*bischloromethyltetrahydrofuran* (III).

It was expected that the di-*p*-toluenesulphonate (II) would give rise to the diamine, 2 : 5-bisaminomethyltetrahydrofuran (IV), on treatment with methyl-alcoholic ammonia. The compound isolated, however, was not a diamine but a substance of empirical formula $C_6H_{11}ON$ to which the dicyclic structure (V) has been assigned. The argument in support of this is as follows. The compound was basic and very hygroscopic, and on exposure to air readily formed a crystalline *carbonate*. It was a monoacidic base, and the crystalline *hydrochloride*, *oxalate*, *picrate*, and p-*toluenesulphonate* were prepared. Treatment of the compound with nitrous acid


(I.)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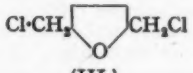
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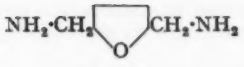
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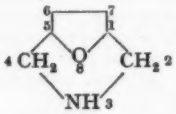
(V.)

(VI.)

(VII.)

(Ts = *p*-Me·C_6H_4·SO_2·)

yielded a *nitrosoamine* which gave the Liebermann reaction, thus showing the nitrogen atom in the molecule to be secondary and probably involved in a ring. Treatment of the compound $C_6H_{11}ON$ with acetic anhydride in methyl alcohol gave only the crystalline acetate, and not the expected *N*-acetyl derivative, but acetylation with acetic anhydride and sodium acetate gave a liquid which was not hydrolysed readily by aqueous sodium hydroxide, showing it to be an N-*acetyl* derivative. Although the amine absorbed bromine and decolourised alkaline permanganate slowly, it was shown to be fully saturated by the fact that no catalytic hydrogenation occurred in the presence of Raney nickel.

These experiments show that in the compound $C_6H_{11}ON$ the oxygen atom must be present as part of the tetrahydrofuran ring; and the nitrogen atom, since the compound forms a nitrosoamine, must be involved in a second ring structure. The compound $C_6H_{11}ON$ must be 8-*oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane* (V).

Treatment of 2 : 5-bischloromethyltetrahydrofuran (III) with methyl-alcoholic ammonia gave the same products as were formed when 2 : 5-bishydroxymethyltetrahydrofuran di-*p*-toluenesulphonate was treated in a similar way, although the yield of (V) was somewhat lower.

A diamino-derivative of tetrahydrofuran was obtained when 2 : 5-bischloromethyltetrahydrofuran was treated with a secondary amine. Thus, with diethylamine at 160° under pressure, it gave 2 : 5-*bis*(*diethylaminomethyl*)*tetrahydrofuran* (VI), a pale yellow liquid which on treatment with methyl iodide gave a crystalline *dimethiodide*. It seems probable, therefore, that a bisaminomethyl-derivative of tetrahydrofuran can be obtained only when no elimination of ammonia or amine can take place between the two side chains.

2 : 5-Bishydroxymethyltetrahydrofuran di-*p*-toluenesulphonate was difficult to hydrolyse with alkali in aqueous solution owing to its low solubility. Some hydrolysis did occur, however, when it was heated at 180° under pressure, and 2 : 5-bishydroxymethyltetrahydrofuran was isolated in small yield. Boiling with aqueous-alcoholic alkali on the other hand readily hydrolysed the compound to 2 : 5-*bisethoxymethyltetrahydrofuran* (VII).

EXPERIMENTAL.

2 : 5-*Bishydroxymethyltetrahydrofuran Di*-p-*toluenesulphonate*.—2 : 5-Bishydroxymethyltetrahydrofuran (27 g.) was dissolved in dry pyridine (250 c.c.) and cooled to 0°. A solution of *p*-toluenesulphonyl chloride in pyridine (85 g in 100 c.c.; 2·2 mols.) was added to the cooled solution with stirring and

the mixture kept for 24 hours. It was then poured into water and the crystalline p-*toluenesulphonate* filtered off, washed with water until free from pyridine, and dried. It recrystallised from alcohol in needles, m. p. 127·5—128°. Yield, 77 g. (90%) (Found: C, 54·6; H, 5·2; S, 13·7. $C_{20}H_{24}O_7S_2$ requires C, 54·6; H, 5·4; S, 14·5%).

2 : 5-*Bischloromethyltetrahydrofuran.*—2 : 5-Bishydroxymethyltetrahydrofuran (7·6 g.) was dissolved in dry pyridine (14·5 c.c.), and anhydrous magnesium sulphate (2 g.) added. Thionyl chloride (13·6 c.c.) was added dropwise to the stirred solution cooled to 0°, and the mixture heated at 50° until evolution of sulphur dioxide had subsided; the temperature was then raised to 100° for ½ hour. The dark syrupy liquid was then poured on ice and extracted with ether. The extract was neutralised with sodium carbonate solution, washed with water, and dried ($MgSO_4$). Evaporation of the ether gave 2 : 5-*bischloromethyltetrahydrofuran* which distilled at 69° (bath temp.)/0·03 mm., 130° (bath temp.)/15 mm., as a pale yellow mobile liquid, $n_D^{16°}$ 1·4840. Yield, 5·5 g. (56%) (Found: C, 43·0; H, 5·9; Cl, 43·8. $C_6H_{10}OCl_2$ requires C, 42·6; H, 5·9; Cl, 42·1%).

8-*Oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane.*—2 : 5-Bishydroxymethyltetrahydrofuran di-*p*-toluenesulphonate (50 g.) was heated with dry methyl alcohol (1 l. saturated with ammonia at 0°) under pressure at 160° for 36 hours. After evaporation of the alcohol under reduced pressure, the residue was hydrolysed with barium hydroxide solution (54 g. in 500 c.c. of water) at 100° for 1 hour in an atmosphere of nitrogen. After evaporation of the water under reduced pressure, the residue was freed from last traces of water by azeotropic distillation with benzene and thereafter the residue was extracted with boiling chloroform. Evaporation of the solvent gave a syrup (6·0 g.). From this, 8-*oxa*-3-*aza*bicyclo[3 : 2 : 1]*octane* (V) distilled as a colourless liquid (4·5 g.), b. p. 176—178°/760 mm., $n_D^{15°}$ 1·4883 [Found: N, 11·3; *M* (ebullioscopic), 115. $C_6H_{11}ON$ requires N, 12·5%; *M*, 113]. Analysis was extremely difficult owing to the ease with which the compound combines with carbon dioxide.

A second fraction, which distilled at 135—140° (bath temp.)/0·02 mm. as a colourless syrup (1·1 g.) showing $n_D^{20°}$ 1·5014, has not yet been identified.

8-Oxa-3-aza*bicyclo*[3 : 2 : 1]octane was basic to litmus and to brilliant-yellow, and was very hygroscopic. It decolourised alkaline permanganate slowly and absorbed bromine, but in spite of this, no hydrogenation occurred in the presence of Raney nickel and the substance was recovered unchanged. On exposure to air, a crystalline *carbonate* was formed. This was very deliquescent and when left exposed to the atmosphere overnight completely volatilised. It was recrystallised from dry light petroleum–dioxan and then had m. p. 24—25° but was very difficult to analyse [Found: N, 10·1; equiv. (by titration with hydrochloric acid), 158. $C_6H_{11}ON,\frac{1}{2}H_2CO_3$ requires N, 9·7%; equiv., 144]. Evaporation of the aqueous solution from the titration gave the crystalline *hydrochloride* which on recrystallisation from alcohol–ether had m. p. 197—199° (Found: C, 47·7; H, 7·5. $C_6H_{11}ON,HCl$ requires C, 48·2; H, 8·0%).

The *oxalate*, prepared from alcoholic solutions of the base (0·1 g.) and oxalic acid (0·7 g.), recrystallised from alcohol in prisms, m. p. 266—267° (Found: C, 52·8; H, 7·6; N, 9·1. $C_{14}H_{24}O_6N_2$ requires C, 53·2; H, 7·6; N, 8·9%). The *picrate* recrystallised from water in plates, m. p. 188—189° (Found: C, 42·0; H, 4·1; N, 16·0. $C_{12}H_{14}O_8N_4$ requires C, 42·1; H, 4·1; N, 16·3%). The p-*toluenesulphonate*, prepared by mixing alcoholic solutions of the base (0·1 g.) and *p*-toluenesulphonic acid (0·1 g.) and adding ether, recrystallised from alcohol–ether in plates, m. p. 204—205° (Found: C, 54·8; H, 6·4; N, 5·1. $C_{13}H_{19}O_4NS$ requires C, 54·8; H, 6·6; N, 4·9%).

The base (0·36 g.) was dissolved in glacial acetic acid (3 c.c.) and 30% potassium nitrite solution (2·5 c.c.) added. After being kept overnight, the solution was evaporated and the residue dried and extracted with ether. Evaporation of the ethereal extract gave a syrup (0·3 g.) which crystallised on refrigeration. The *nitrosoamine* recrystallised from absolute ether in plates, m. p. 39—40·5° (Found: C, 50·8; H, 6·9; N, 19·9. $C_6H_{10}O_2N_2$ requires C, 50·7; H, 7·0; N, 19·7%). The nitrosoamine on treatment with phenol and concentrated sulphuric acid gave the characteristic Liebermann reaction.

Acetylation of (V).—(*a*) The base (0·7 g.) was dissolved in dry methyl alcohol (5 c.c.) and acetic anhydride (0·31 c.c.) added. The solution was kept for 12 hours and then evaporated under reduced pressure at room temperature. A hygroscopic crystalline residue was obtained which recrystallised from ether in needles, m. p. 133—134·5. Yield, 0·2 g. (Found: C, 55·7; H, 8·5. $C_8H_{15}O_2N$ requires C, 55·5; H, 8·7%). It was the *acetate* of (V).

(*b*) The base (0·5 g.) was dissolved in acetic anhydride (5 c.c.) and fused sodium acetate (0·5 g.) added. The solution was boiled under reflux for 5 minutes and then poured into water. The acid was neutralised with sodium hydrogen carbonate and the solution extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated. A syrup (0·7 g.) was obtained, which distilled at 140° (bath temp.)/0·02 mm. as a colourless liquid, $n_D^{15°}$ 1·5098; it was the N-*acetyl* derivative of (V) [Found: C, 61·4; H, 7·9; *O*-Ac (by treatment with N/10-NaOH at 60°), nil. $C_8H_{13}O_2N$ requires C, 61·9; H, 8·4%; *O*-Ac, nil].

Attempted Acetolysis of (V).—The base (0·6 g.) was boiled under reflux with acetic anhydride (6 c.c.) and zinc chloride (0·1 g.) for 2 hours. The excess of acetic anhydride was distilled off and the residual oil poured into water. The acid was neutralised with sodium hydrogen carbonate and the solution extracted with chloroform. The extract was dried ($MgSO_4$), and, on evaporation of the solvent, a syrup (0·4 g.) was obtained which distilled at 135° (bath temp.)/0·01 mm. and had $n_D^{15°}$ 1·4989; it was the *N*-acetyl derivative, obtained above (Found: N, 8·3; *O*-Ac, nil. Calc. for $C_8H_{13}O_2N$: N, 9·0%; *O*-Ac, nil.).

Treatment of 2 : 5-*Bischloromethyltetrahydrofuran with Methyl-alcoholic Ammonia.*—The compound (30 g.) was dissolved in dry methyl-alcoholic ammonia (700 c.c. saturated at 0°) and heated at 150° for 72 hours. After evaporation of the alcohol under reduced pressure, the residue was hydrolysed with a solution of barium hydroxide (62 g. in 200 c.c. of water) at 100° for 1 hour in an atmosphere of nitrogen. After evaporation of the water under reduced pressure, the residue was freed from last traces of water by distillation with benzene and the residue extracted with boiling chloroform. Evaporation of the solvent gave a syrup (4·2 g.) from which 8-oxa-3-aza*bicyclo*[3 : 2 : 1]octane distilled at 97—100°/15 mm. (nitrogen), $n_D^{20°}$ 1·4840. A *p*-toluenesulphonate was obtained, m. p. 204—205° alone or in admixture with that obtained previously.

Treatment of 2 : 5-*Bischloromethyltetrahydrofuran with Diethylamine.*—The compound (2 g.) was heated in a sealed tube with excess of diethylamine (10 c.c.) at 165° for 8 hours, during which time crystals of diethylamine hydrochloride separated. The excess of diethylamine was evaporated and the residue acidified with dilute hydrochloric acid. Some unchanged starting material separated at this stage and was removed by extraction with ether. The aqueous portion was then made alkaline and the oil which separated extracted with ether. Evaporation of the solvent after drying ($MgSO_4$) gave 2 : 5-*bis*(*diethylaminomethyl*)*tetrahydrofuran*, which distilled at 134° (bath temp.)/15 mm. as a colourless liquid showing $n_D^{18°}$ 1·4639. Yield, 1 g. (46·5%) (Found : N, 11·9. $C_{14}H_{30}ON_2$ requires N, 11·6%).

2 : 5-Bis(diethylaminomethyl)tetrahydrofuran (0·1 g.) was treated with excess methyl iodide at room temperature for one hour. On evaporation of the methyl iodide, an oil was obtained which crystallised on trituration with alcohol. The *dimethiodide* recrystallised from alcohol in clusters of needles, m. p. 187—188·5°. Yield, almost quantitative (Found : C, 36·6; H, 6·9. $C_{16}H_{34}ON_2I_2$ requires C, 36·5; H, 6·8%).

Action of Alkali on 2 : 5-*Bishydroxymethyltetrahydrofuran Di*-p-*toluenesulphonate.*—The compound (16 g.) was boiled under reflux with a solution of sodium hydroxide (3·5 g. in 500 c.c. of water) for 2 days. At the end of this time no reaction had occurred. The above mixture was then heated under pressure at 150—180° for 4 hours. Unchanged di-*p*-toluenesulphonate was filtered off (14 g.) and excess of alkali neutralised with carbon dioxide. The solution was evaporated to dryness under reduced pressure and the residue extracted with chloroform. Evaporation of the solvent gave a syrup (0·5 g.) which distilled at 140° (bath temp.)/0·08 mm. and had $n_D^{18°}$ 1·4902; it was 2 : 5-bishydroxymethyltetrahydrofuran, identified as the crystalline di-*p*-toluenesulphonate which, on recrystallisation from alcohol, had m. p. 126—127° alone or in admixture with an authentic specimen.

The compound (25 g.) was dissolved in alcohol (250 c.c.) and a solution of sodium hydroxide (5 g. in 50 c.c. of water) added. After 24 hours' boiling under reflux, the alcohol was evaporated and water (100 c.c.) added. The solution was then extracted with ether and the extract dried ($MgSO_4$). After evaporation of the solvent 2 : 5-*bisethoxymethyltetrahydrofuran* distilled at 210°/760 mm. as a colourless mobile liquid, $n_D^{19°}$ 1·4356. Yield, 4·7 g. (40%) (Found : C, 63·6; H, 10·2. $C_{10}H_{20}O_3$ requires C, 63·8; H, 10·6%).

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39. *The Isolation and Some Properties of Dehydro-*l*-ascorbic Acid.*

By J. Kenyon and N. Munro.

A crystalline solid possessing the characteristics of anhydrous dehydro-*l*-ascorbic acid has been isolated, the preparation together with that of two derivatives being described. A study of its properties has confirmed the view that in aqueous solution dehydro-*l*-ascorbic acid exists as a hydrate. In addition to those of 2 : 3-diketo-*l*-gulonic acid, a second series of salts has been obtained from dehydroascorbic acid. A possible structure of these salts is discussed.

The chemistry of dehydro-*l*-ascorbic acid—the primary reversible oxidation product of vitamin C—has hitherto been mainly investigated by utilising solutions of the freshly oxidised vitamin. In the course of early work on the constitution of *l*-ascorbic acid (Herbert *et al.*, *J.*, 1933, 1270), formulation of the dehydro-compound as the γ-lactone of 2 : 3-diketo-*l*-gulonic acid was established, absorption spectra data suggesting that hydration of the keto-groups in aqueous solution was probable. The labile nature of the substance has, however, prevented its isolation hitherto in a pure state, although Hirst and Woodward (*vide* Crook and Morgan, *Biochem. J.*, 1944, **38**, 10) have prepared it as a solid from which, by treatment with hydrogen sulphide, *l*-ascorbic acid could be regenerated in 65—75% yield.

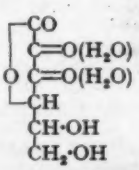
During the course of renewed investigation on this problem it has been found that when the solid product obtained by the method of Hirst and Woodward (*loc. cit.*) is intensively dried and dissolved in ethanol at room temperature, the solution on standing deposits a crystalline colourless compound which has the characteristics of anhydrous *dehydroascorbic acid*, although its existence as a polymer is not excluded. The absence of colour in an αα-diketone is surprising, but that the same property is found with 3 : 4-diketo-2 : 5-dicarbethoxytetrahydrofuran (Johnson and Johns, *Amer. Chem. J.*, 1906, **36**, 290), the structure of which in many respects resembles that of dehydroascorbic acid, is worthy of note.

Owing to its insolubility in neutral solvents measurement of many physical constants has been impossible. It was found necessary to warm to 60° to achieve immediate solution of anhydrous dehydroascorbic acid in water. On evaporation of the resultant solution a viscous syrup was obtained from which the anhydrous material could only be recovered, in low yield, by application of the drying procedure already mentioned.

The hydration hypothesis is thus confirmed, the syrupy product representing a hydrate form in which dehydroascorbic acid normally exists. In contrast to the anhydrous form, the hydrate is readily soluble in many organic solvents such as alcohols.

Acetylation of anhydrous dehydroascorbic acid with acetic anhydride and sulphuric acid yielded a *diacetyl* derivative. This compound, which was also colourless, was not dissolved by water even on boiling. The behaviour of aqueous solutions prepared from anhydrous dehydroascorbic acid was similar to that of solutions of freshly oxidised *l*-ascorbic acid; *e.g.*, hydrogen sulphide effected reduction to *l*-ascorbic acid which was isolated in good yield (crude, 90%). In water alone, the opening of the lactone ring to give free 2 : 3-diketo-*l*-gulonic acid was found to be extremely rapid in its initial stages. Immediately after preparation the solutions were invariably slightly acid, having pH 3·0—3·5. In optical rotation measurements and in titrimetric assays of *l*-ascorbic acid regenerated by hydrogen sulphide it was necessary to use as solvent a buffer solution of pH 3·5 in order to obtain maximum values. The characteristic osazone of 2 : 3-diketogulonic acid, which is described in the literature (Herbert *et al.*, *loc. cit.*; Drum, Scarborough, and Stewart, *Biochem. J.*, 1937, **31**, 1874; Penney and Zilva, *ibid.*, 1943, **37**, 39, 403) and is also obtainable from *l*-ascorbic acid and oxidised ascorbic acid, was produced by condensation with 2 : 4-dinitrophenylhydrazine in aqueous alcohol when starting with crystalline anhydrous dehydroascorbic acid.

The increase in acidity and accompanying mutarotation in oxidised *l*-ascorbic acid solutions has been studied by many workers (Herbert *et al.*, *loc. cit.*; Penney and Zilva, *loc. cit.*; Borsook, Davenport, Jeffreys, and Warner, *J. Biol. Chem.*, 1937, **117**, 237; Ghosh and Rakshit, *Biochem. Z.*, 1938, **299**, 394; Rosenfeld, *J. Biol. Chem.*, 1943, **150**, 281), the production of free 2 : 3-diketogulonic acid being later demonstrated by the isolation of the corresponding calcium and barium salts by Penney and Zilva (*Biochem. J.*, 1945, **39**, 1). We have similarly prepared the barium salt from solutions of crystalline dehydroascorbic acid after partial neutralisation with sodium hydroxide. It has been found, however, that in aqueous solution anhydrous dehydroascorbic acid titrates with alkali as a dibasic acid though its rearrangement to give the necessary H^+ ions is slow and the titration has to be carried out potentiometrically and in an indirect manner. The source of the second H^+ ion has been elucidated by the preparation of a further series of salts of the formula $C_6H_6O_7M$ (M = Na_2, Ca, Ba). These are orange-red in colour, the *disodium* salt giving an orange-coloured aqueous solution while the *calcium* and *barium* salts were almost insoluble in water. All were soluble in excess of mineral or acetic acid giving yellow solutions which possessed considerable reducing activity, taking up two equivalents of oxidising agent on treatment with bromine or iodine and slowly reducing 2 : 6-dichlorophenolindophenol to a like extent. This reducing activity was unaffected by treatment with hydrogen sulphide. The structure of the salts would be explained by the theory of Ghosh (*loc. cit.*); this author also observed that dehydroascorbic acid reacts with more than one equivalent of alkali and suggested that the ions might be derived severally from enolisation of the second keto-grouping and from opening of the lactone ring. It is now apparent, of course, that if this be the explanation, opening of the lactone ring must preceed enolisation (formulæ I, II, III).



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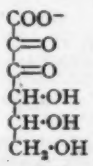

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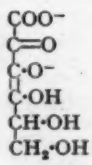

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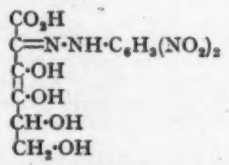


(IV.)

The development of yellow colour in oxidised *l*-ascorbic acid solutions on keeping is well known, and Rosenfeld (*loc. cit.*) has found a correlation between the colour intensity and the reducing activity of such solutions.

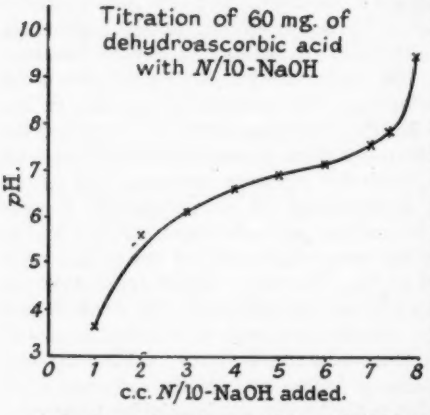
Further evidence for the enol–acid structure is the fact that only one molecule of 2 : 4-dinitrophenylhydrazine will condense with the free acid (III) obtained in solution by treatment of the salts with sulphuric acid in ethanol; the resulting dark red dinitrophenylhydrazone has the formula $C_{12}H_{12}O_{10}N_4$, which is in accord with the postulated structure (IV).

It is, however, difficult to understand how a compound having such a structure could give only oxalic and threonic acids on decomposition as already established with dehydroascorbic acid (Hirst and Reynolds, *Nature*, 1932, **129**, 576; **130**, 888; Herbert *et al.*, *loc. cit.*).

Experimental.

Anhydrous Dehydro-l-ascorbic Acid.—Pure *l*-ascorbic acid (8·8 g.) was shaken with resublimed iodine (12·4 g.; 1·96 mols.) in methanol (75 c.c.; water content, 0·5%). Excess of precipitated lead carbonate (30—35 g.) was gradually added until completion of the reaction, *i.e.*, until a colourless solution was obtained after settling of the lead salts. The solution was filtered and the residues were washed with methanol (50 c.c.). Traces of lead remaining in solution were precipitated by a few bubbles of hydrogen sulphide, excess of this reagent being immediately removed by a current of air. Failure to remove excess of hydrogen sulphide with the minimum of delay results in the presence of small amounts of sulphur in the final product. The dehydroascorbic acid–methanol solution was filtered from lead sulphide through kieselguhr and subsequently evaporated at *ca.* 30—40° (bath temp.)/20 mm. to a syrup. The bath temperature was then gradually raised (during 20 minutes) to 100° and maintained thereat for a further hour before cooling to room temperature, the dehydroascorbic acid being kept under vacuum. After cooling, the resulting crisp glass was shaken with absolute alcohol (30 c.c.) and the solution kept at 0° for 2 days. The microcrystalline *dehydroascorbic acid* was collected, washed twice with absolute alcohol (25 c.c.) followed by cold distilled water (10 c.c.) and finally with a further 50 c.c. of absolute alcohol, before being dried in a vacuum. Yield, 2·0 g. (Found: C, 41·2, 40·9; H, 3·5, 3·8. $C_6H_6O_6$ requires C, 41·4; H, 3·5%).

Freshly prepared anhydrous dehydroascorbic acid was white, and had m. p. 225° (decomp.); after 6 months at ordinary temperature it had become yellow–brown and then had m. p. 204—205° (decomp.). Purification by crystallisation was not found possible owing to its insolubility in all available neutral organic solvents. It dissolved readily in basic solvents such as pyridine but could not be recovered. Complete and immediate solution in water was only obtained on warming to 60°; no solid product separated on cooling.



Properties of Dehydroascorbic Acid in Aqueous Solution.—(a) *Regeneration of ascorbic acid by hydrogen sulphide.* Anhydrous dehydroascorbic acid (2 g.) was dissolved in water (100 c.c.) at 60°; the solution was rapidly cooled to 0° and a current of hydrogen sulphide passed for 90 minutes, the temperature meanwhile being allowed to rise to 14°. The solution was kept in a closed vessel for 2 days before the excess of hydrogen sulphide was removed in a current of carbon dioxide. The precipitated sulphur was filtered off and washed with a further 100 c.c. of water, and the combined filtrates were evaporated at 30° (bath temp.)/10 mm. in a current of carbon dioxide. The slightly yellow residue was triturated with acetone (30 c.c.), filtered off, and dried. Yield, 1·8 g. (90%); m. p. 173—176° (decomp.); content of *l*-ascorbic acid by iodine titration, 91%. By recrystallisation from methanol–ether–petrol the purity was raised to 99%; m. p. alone and mixed with authentic *l*-ascorbic acid, 188—189° (decomp.).

Anhydrous dehydroascorbic acid (100 mg.) was dissolved with warming in 15 c.c. of a phthalate–hydrochloric acid buffer of pH 3·5. A further 15 c.c. of cold buffer were immediately added and the solution was saturated with hydrogen sulphide during ¾ hour before being kept corked for 12 hours. Excess of hydrogen sulphide was removed by a current of carbon dioxide (—ve test to lead acetate paper), one drop of glacial acetic acid added, and the solution titrated with N/10-iodine (titre, 11·0 c.c.; calc., 11·4 c.c.).

This experiment was repeated, the buffer solution being replaced by distilled water (titre, 10·5 c.c.).

(b) *Specific rotation.* A 1% dehydroascorbic acid solution prepared by dissolving the anhydrous material in a phthalate–hydrochloric acid buffer of pH 3·5 at 60° and immediately cooling to 20°, had $[\alpha]_D^{20°}$ +56° (initial); +53·5° (after 2 hours); +19·0° (3 days); −2·0° (5 days); −6·0° (6 days). The solution had become red–yellow when readings were discontinued. It was found necessary to cool the freshly dissolved dehydroascorbic acid as rapidly as possible in an ice-bath, otherwise a slightly lower initial specific rotation was obtained.

A 1% solution similarly prepared in distilled water had $[\alpha]_D^{20°}$ +50° (initial); +44° (after 2 hours); +23° (2 days); +16° (3 days); 0° (6 days).

(c) *Acidity of dehydroascorbic acid and titration with alkali.* A 1% aqueous solution obtained on warming followed by cooling to 20° had pH 3·37 (initial); 2·08 (after 6 days). Anhydrous dehydroascorbic acid (100 mg.) likewise dissolved in distilled water (10 c.c.) required 0·4 c.c. of N/20-sodium hydroxide for titration to methyl-red. Anhydrous dehydroascorbic acid (0·600 g.) was dissolved in hot distilled water and the solution made up to 100 c.c. Aliquots (10 c.c.) were removed and quantities of N/10-sodium hydroxide (from 1 to 8 c.c.) added to each before these were warmed, under nitrogen, to 70—80° for 20 minutes. Each solution was then cooled, made up to 25 c.c. with water, and the pH measured electrometrically.

No rapid increase in alkalinity was found until just over 2 equivs. of alkali were present. The slight discrepancy is probably due to the production of acid breakdown-products in the more alkaline solutions as has been observed by other investigators. Another experiment was carried out in which the pH was measured immediately. Downward drifts of pH at values over 6 were encountered; these were slow and sustained, and the foregoing procedure was therefore adopted. Attempts to measure the intensity of yellow–red colour produced in the more alkaline solutions failed owing to fading.

(d) *Recovery of anhydrous dehydroascorbic acid.* Anhydrous dehydroascorbic acid (1 g.) was dissolved with gentle warming in distilled water (30 c.c.) and the resultant solution immediately evaporated

below 30°, first at 10 mm. and finally at 0·1 mm. A very viscous, pale yellow syrup was obtained which did not crystallise on being kept for 1 week at 0°. 1·089 G. of syrup dried to constant weight at 90—100° in a vacuum lost 0·160 g. (14·7%). The resultant reddish glass was powdered, shaken with 20 c.c. of absolute alcohol, and kept at 0° for 3 days. 60 Mg. of anhydrous dehydroascorbic acid [m. p. 221° (decomp.)] were recovered.

Derivatives of Anhydrous Dehydroascorbic Acid.—*2 : 4-Dinitrophenylosazone.* The acid (0·5 g.) was dissolved with gentle warming in water (4 c.c.), ethanol (15 c.c.) added, and the solution treated with 2 : 4-dinitrophenylhydrazine (1·0 g. + 2 c.c. of concentrated sulphuric acid + 20 c.c. of ethanol). The osazone was collected next day and well washed with ethanol before being dried; m. p. 282° (decomp.) alone and when mixed with an authentic osazone prepared from *l*-ascorbic acid (Found : N, 21·0%). *Acetylation.* The acid (0·5 g.) was gently warmed with acetic anhydride (15 c.c.) containing 2 drops of concentrated sulphuric acid until solution was complete. The solution was poured into cold distilled water (50 c.c.) and stirred for 5 minutes to precipitate the white *acetyl* derivative which was washed by decantation with cold water until free from acid and finally boiled with 50 c.c. of water, filtered off, and dried. Yield, 0·45 g.; m. p. 246—247° (decomp.; darkens and shrinks *ca.* 230°). It can be recrystallised from aqueous pyridine, m. p. unchanged (Found : C, 46·4, 46·2; H, 3·8, 3·7. $C_{10}H_{10}O_8$ requires C, 46·5; H, 3·9%).

Preparation of Salts from Dehydroascorbic Acid.—Barium diketogulonate. To a solution of anhydrous dehydroascorbic acid (0·87 g.) in water (6 c.c.) N-sodium hydroxide (5 c.c.) was added gradually. The yellow solution was adjusted to pH 3 with N-hydriodic acid, when it became colourless; barium iodide (0·8 g.) was then added. The barium diketogulonate which separated after the addition of ethanol (100 c.c.) was filtered off, washed with ethanol and ether, and dried in a vacuum (Found : Ba, 21·0. Calc. : Ba, 20·7%). The salt gradually turned yellow in a vacuum desiccator at room temperature.

Salts from dibasic dehydroascorbic acid. A solution of anhydrous dehydroascorbic acid (1·74 g.) in warm distilled water (5 c.c.) and methanol (25 c.c.) was gradually stirred into 1·6 g. (4 equivs.) of sodium hydroxide in methanol (100 c.c.). The *disodium* salt which appeared as an orange precipitate was collected and washed with 3 × 50 c.c. of methanol, being well stirred in the filter each time. This hygroscopic salt was immediately dried in a vacuum desiccator then triturated with more methanol (25 c.c.), collected again, and redried to constant weight in a vacuum, first at ordinary temperature and finally at 60°. Yield, 1·5 g. (Found : Na, 19·7. $C_6H_6O_7Na_2$ requires Na, 19·5%).

This disodium salt (1·0 g.) was dissolved in cold distilled water (10 c.c.) and a solution of 0·42 g. (0·8 equiv.) of calcium chloride in water (10 c.c.) stirred in. The *calcium* salt was precipitated as a gelatinous solid which was filtered off with some difficulty. Washing was carried out by stirring in the filter with 50 c.c. of water in 2 parts. The salt was dried in a vacuum, first at 20° and finally at 100° (Found : C, 31·7; H, 2·8; Ca, 17·5. $C_6H_6O_7Ca$ requires C, 31·3; H, 2·6; Ca, 17·4%). The *barium* salt was prepared in a similar way using 1·0 g. of disodium salt and 0·7 g. of barium chloride (Found : Ba, 42·7. $C_6H_6O_7Ba$ requires Ba, 41·8%).

The calcium and barium salts dissolved in excess of calcium or barium chloride solution to give dark red solutions, and it was for this reason that less than the calculated quantities of these reagents were used in their preparation.

The disodium salt (0·8 g.) was stirred in ethanol (20 c.c.) containing 4—5 drops of concentrated sulphuric acid until reaction was complete. The residual sodium sulphate was filtered off, and excess of alcoholic 2 : 4-dinitrophenylhydrazine (1·0 g. + 2 c.c. of concentrated sulphuric acid + 20 c.c. of ethanol) added. After 4 days at ordinary temperature, the dark red derivative was collected, washed with ethanol, and dried in a vacuum. Yield, 0·25 g.; m. p. 208° (decomp.) (Found : C, 39·5; H, 3·1; N, 15·0. $C_{12}H_{12}O_{10}N_4$ requires C, 38·7; H, 3·2; N, 15·1%).

Reducing action of the disodium and the calcium salt. To a freshly prepared solution of the calcium salt (0·125 g.) in hydrochloric acid (25 c.c. of N/5), bromate–bromide solution (20 c.c. of N/10) was added. After ½ hour, excess of potassium iodide solution was added and the solution titrated with N/10-thiosulphate. (N/10-Bromine uptake, 10·5 c.c. Calc. for 2 equivs. : 10·8 c.c.)

Disodium salt (0·104 g.) was dissolved in the calculated quantity (8·8 c.c.) of N/10-hydrochloric acid for exact neutralisation. N/10-Iodine (20 c.c.) was added and the solution kept for 15 minutes before titration with N/10-thiosulphate. (N/10-Iodine uptake, 9·1 c.c. Calc. : 8·8 c.c.)

5 C.c. of a phosphate–citrate buffer of pH 3·5 containing 1 mg. of disodium salt were titrated with standard 2 : 6-dichlorophenolindophenol (1 c.c. = 0·30 mg. of ascorbic acid). No sharp visual end point was obtained, dye decolourisation becoming progressively slower. After 20 minutes the dye uptake was *ca.* 2 equivs. (2·3 c.c.), further reduction being negligible. Saturation of the disodium salt solution with hydrogen sulphide for 2 hours followed by removal of excess by means of carbon dioxide had no effect on the titration values subsequently obtained.

In these titrimetric oxidations freshly prepared salts were used, their reducing power having been observed to deteriorate on keeping.

Thanks are due to the Directors of Messrs. Roche Products Ltd. for facilities to one of us (N. M.) and to Dr. F. Bergel for helpful advice in the preparation of this paper.

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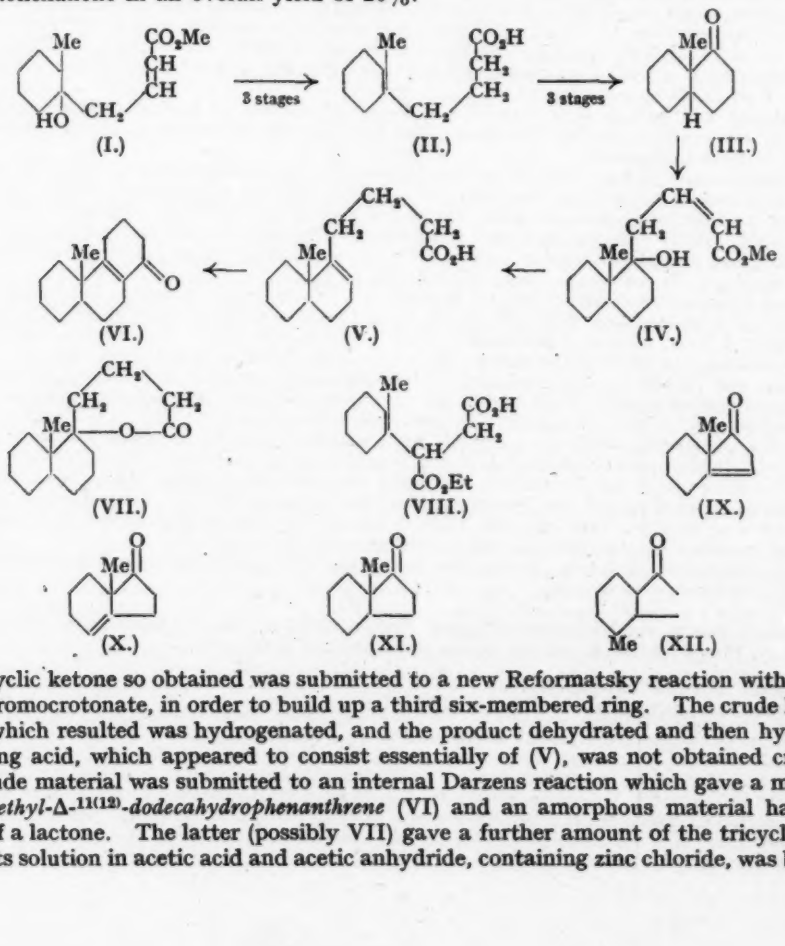
40. *Synthetic Studies in the Steroid Series. Part I. Use of Methyl γ-Bromocrotonate in the Synthesis of Fused-ring Hydroaromatic Ketones.*

By J. W. Cook and R. Philip.

cis-9-Methyl-1-decalone (III), an intermediate suitable for the synthesis of compounds of the aetiocholane series, has been prepared by a new method and converted by a series of reactions similar to that used in its preparation into 1-*keto*-13-*methyl*-$\Delta^{11(12)}$-*dodecahydrophenanthrene* (VI). By Johnson's extension of the Stobbe reaction, 2-methyl*cyclo*hexanone has been transformed into a methyl-1-hydrindanone (probably XII).

Cook and Schoental (*J.*, 1945, 288) described a simple synthesis of a hydroaromatic ketone, based on Ziegler's elegant method of preparation of methyl γ-bromocrotonate and its use in the Reformatsky reaction (*Annalen*, 1943, **551**, 80, 120). The extension to other hydroaromatic systems was foreshadowed, and some preliminary work in this field is now recorded in view of the use of very similar methods by Bachmann and Wendler (*J. Amer. Chem. Soc.*, 1946, **68**, 2580). Our work, which has obvious possibilities in the synthesis of fully reduced compounds of the steroid group, is being extended in collaboration with Dr. S. H. Tucker and Mr. G. W. Crosbie.

cis-9-Methyl-1-decalone (III) has been prepared by a variety of methods during the past decade; in many of them an intermediate is γ-(2-methyl*cyclo*hex-1-enyl)butyric acid (II), which is cyclised to 9-methyl-1-octalone by a process developed by Cook and Lawrence (*J.*, 1935, 1637; 1937, 817). In the present work this intermediate acid has been prepared by condensing 2-methyl*cyclo*hexanone with methyl γ-bromocrotonate and zinc to give the hydroxy-ester (I); this was hydrogenated and the resulting saturated hydroxy-ester was dehydrated to give the ester of the required acid (II). By this route, *cis*-9-methyl-1-decalone was obtained from 2-methyl*cyclo*hexanone in an overall yield of 20%.



The dicyclic ketone so obtained was submitted to a new Reformatsky reaction with zinc and methyl γ-bromocrotonate, in order to build up a third six-membered ring. The crude hydroxy-ester (IV) which resulted was hydrogenated, and the product dehydrated and then hydrolysed. The resulting acid, which appeared to consist essentially of (V), was not obtained crystalline and the crude material was submitted to an internal Darzens reaction which gave a mixture of 1-*keto*-13-*methyl*-$\Delta^{11(12)}$-*dodecahydrophenanthrene* (VI) and an amorphous material having the character of a lactone. The latter (possibly VII) gave a further amount of the tricyclic ketone (VI) when its solution in acetic acid and acetic anhydride, containing zinc chloride, was boiled for

5 hours. The intermediate products in this series of reactions have not yet been characterised, and the structure of the ketone (VI) requires confirmation in view of the possibility of methyl migration in the dehydration of the hydroxy-ester (IV).

The ketone (VI), if available in sufficient quantity, may conceivably be converted into 1-keto-2 : 13-dimethylperhydrophenanthrene, from which a sterol ring system might be elaborated by building on a five-membered ring. For this last process several possible methods are available, of which a particularly promising one is the modified Stobbe reaction and ring-closure devised by Johnson *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 1360, 1366). As a model for this, we have condensed 2-methyl*cyclo*hexanone with ethyl succinate by means of potassium *tert.*-butoxide. This led to the *half-ester* (VIII or an isomeride), which was converted by zinc chloride in acetic acid and acetic anhydride and then hydrochloric acid into an unsaturated ketone which, from the m. p. of its *semicarbazone*, was clearly different from the ketone (IX or X) synthesised by Chuang, Tien, and Ma (*Ber.*, 1936, **69**, 1494). Hydrogenation of our ketone gave a saturated ketone of which the semicarbazone melted at a temperature (210°) slightly lower than the figure given by Chuang, Tien, and Ma for the semicarbazone of their corresponding saturated ketone. This m. p. was, however, much lower than those given by other workers (Kon, Linstead, and Simons, *J.*, 1937, 814; Robinson and Walker, *J.*, 1937, 1160; Bachmann and Kushner, *J. Amer. Chem. Soc.*, 1943, **65**, 1963) for the semicarbazones of the pure *cis*- and *trans*-8-methyl-1-hydrindanones (XI) (*e.g.*, *cis*, 225°; *trans*, 242°). For comparison, therefore, an authentic specimen of *cis*-8-methyl-1-hydrindanone was prepared by degradation of *cis*-9-methyl-1-decalone (III) (cf. Johnson, *J. Amer. Chem. Soc.*, 1943, **65**, 1317; 1944, **66**, 215). Its semicarbazone depressed the m. p. of the semicarbazone of our ketone under examination. This evidence suggests that our ketone is not one of the 8-methyl-1-hydrindanones but a structural isomeride (XII).

Experimental.

New Synthesis of γ-(2-Methylcyclohex-1-enyl)butyric Acid (II).—Pure zinc filings (10 g.), prepared by milling arsenic-free zinc rods, were placed in a flask with a little mercuric chloride and heated over a free flame until a sublimate formed. The activated zinc was covered with benzene (50 c.c.), which was heated to boiling and then cooled. 2-Methyl*cyclo*hexanone (11 g.) and methyl γ-bromocrotonate (21 g.) were then added. A vigorous reaction set in and the solution boiled spontaneously for 5—7 minutes, water-cooling being used as necessary to moderate the reaction. The whole was then boiled by steam-heating for ½ hour, cooled, and the zinc complex decomposed by the addition of ice-cold dilute hydrochloric acid. The product was extracted with ether, and the extract was dried (Na_2SO_4) and distilled. A solution of the distillate (I ; 11 g.), b. p. 170—175°/15 mm., in ethanol (45 c.c.) was shaken with palladium black (0·1 g.) and hydrogen until absorption was complete (13 hours). The saturated hydroxy-ester (9 g.) had b. p. 144—160°/12 mm. For dehydration, a few crystals of iodine were added to this material (6·1 g.) and the liquid was heated almost at its b. p. for ½ hour. Water was liberated. The resulting unsaturated ester was hydrolysed by aqueous methanolic sodium hydroxide at room temperature (24 hours) and the acidic product isolated in the usual way. The crude solid acid (4·9 g.), when pressed on porous porcelain, had m. p. 39° [Elliott and Linstead, *J.*, 1938, 660, give m. p. 44° for γ-(2-methyl*cyclo*hex-1-enyl)butyric acid]. Dehydration of the hydroxy-ester was also effected by anhydrous sodium hydrogen sulphate at 180° in ½ hour. The unsaturated acid (II) was cyclised in the usual way (cf. Cook and Lawrence, *loc. cit.*), The resulting 9-methyloctalone gave a semicarbazone, m. p. 225—226° (Found : C, 65·4; H, 8·5; N, 18·8. Calc. for $C_{12}H_{19}ON_3$: C, 65·1; H, 8·5; N, 19·0%), and the m. p. was not depressed by admixture with an authentic specimen. The unsaturated ketone (4·5 g.) was hydrogenated to *cis*-9-methyl-1-decalone with a palladium-black catalyst. On a larger scale it was found convenient to work under pressure. A solution of the methyloctalone (50 g.) in ethanol (500 c.c.) was agitated at 50° for 6 hours with palladised strontium carbonate (20 g.) and hydrogen (initial pressure, 115 atmospheres). The crude distilled 9-methyl-1-decalone (44 g.), b. p. 108—112°/12 mm., gave a semicarbazone which crystallised from ethanol in colourless needles, m. p. 221—222°, depressed to 204—207° by admixture with the semicarbazone of the unsaturated ketone (Found : C, 64·7; H, 9·5. Calc. for $C_{13}H_{21}ON_3$: C, 64·4; H, 9·4%).

1-*Keto*-13-*methyl*-$\Delta^{11(12)}$-*dodecahydrophenanthrene* (VI).—*cis*-9-Methyl-1-decalone (10 g.) was added to a suspension of amalgamated zinc (10 g.), prepared as described above, in benzene (50 c.c.). To the warm solution methyl γ-bromocrotonate (20 g.) was added. The vigorous reaction was moderated by water-cooling, and was completed by boiling under reflux for ½ hour. The suspension of zinc complex was then cooled and decomposed by stirring with ice-cold dilute hydrochloric acid. Ether was added, and the ether–benzene layer was collected, washed, and dried (Na_2SO_4), and the solvents were distilled on the water-bath. The residual brown oil (containing IV) (14·8 g.) was dissolved in ethanol (100 c.c.) and shaken with hydrogen and palladium-black (0·2 g.) until absorption ceased (10—12 hours). Further absorption was then brought about by addition of more catalyst, the total uptake of hydrogen being 650 c.c. After removal of the solvent from the filtered solution, the residue was heated to boiling for ½ hour, after addition of a few crystals of iodine. The crude unsaturated ester was hydrolysed at room temperature with aqueous methanolic sodium hydroxide. The neutral material which was then recovered by ether extraction was shown to consist of unreacted 9-methyl-1-decalone (*ca.* 4 g.). Acidification of the aqueous alkaline solution gave a brown viscous gum (5·9 g.) which appeared to be a mixture of the unsaturated acid (V) and the lactone (VII).

The crude mixture was treated with thionyl chloride (2·5 c.c.) in pyridine and pure ether and the crude

acid chloride so formed was treated with stannic chloride in carbon disulphide at −15° (compare Cook and Lawrence, *loc. cit.*). After decomposition with ice and hydrochloric acid there separated a brown gum, insoluble in both phases, which solidified when treated with aqueous ethanol. The resulting brown amorphous material (0·8 g.) could not be crystallised. It had the character of a lactone (VII ?), and when its solution in acetic acid (13 c.c.), and acetic anhydride (14 c.c.) containing zinc chloride (60 mg.) was boiled for 4½ hours there was formed a ketonic product, which after distillation at 110—130°/0·3 mm. gave the 2 : 4-dinitrophenylhydrazone, m. p. 225°, described below.

The carbon disulphide solution from which the lactonic material had been separated was distilled, dimethylaniline (2 g.) was added, and the solution then heated at 200° for 3 hours. The neutral material isolated after working up in the usual way was distilled from an air-bath at 105—108°/0·25 mm. and formed a mobile yellow oil (0·7 g.), probably consisting of (VI). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid in red microscopic needles, m. p. 225° (Found : C, 63·7; H, 6·9; N, 14·3. $C_{21}H_{26}O_4N_4$ requires C, 63·3; H, 6·6; N, 14·1%). The *semicarbazone* had m. p. 245—246° (Found : C, 69·7; H, 8·9; N, 15·25. $C_{16}H_{25}ON_3$ requires C, 69·8; H, 9·1, N, 15·3%).

Methyl-1-hydrindanone.—A mixture of 2-methyl*cyclo*hexanone (5·6 g.) and ethyl succinate (13 g.) in *tert.*-butyl alcohol (10 c.c.) was added to an ice-cold solution of potassium *tert.*-butoxide (from 2·15 g. of potassium and 40 c.c. of *tert.*-butyl alcohol). The brownish-red solution was heated under reflux for 40 minutes in an atmosphere of nitrogen and then kept at room temperature for 4 hours. Acidification gave a straw-coloured solution which was concentrated under reduced pressure. Addition of water dissolved the potassium chloride which separated, and sufficient sodium carbonate solution was then added to give an alkaline solution. Undissolved oil was extracted with ether, and the reaction product was precipitated from the aqueous solution by addition of hydrochloric acid. This was extracted with ether and distilled from an air-bath at 0·15 mm. The upper fraction (temperature of bath 130—150°) was a viscous liquid which crystallised after several days. Recrystallisation from ligroin and then hexane gave colourless leaflets, m. p. 99—100°, of *β-carbethoxy-β-(2-methylcyclohex-1-enyl)propionic acid* (VIII) (Found : C, 65·1; H, 8·2. $C_{13}H_{20}O_4$ requires C, 65·0; H, 8·3%). An attempt to effect a similar condensation of 2-methyl*cyclo*hexanone with ethyl glutarate was unsuccessful (cf. Johnson, Johnson, and Petersen, *J. Amer. Chem. Soc.*, 1946, **68**, 1926).

The distilled, but not recrystallised, half-ester (VIII) (2 g.) was dissolved in a mixture of acetic anhydride (28 c.c.), acetic acid (10 c.c.), and an acetic acid solution of zinc chloride (6 c.c. of solution containing 70 mg. of zinc chloride per c.c.). The solution was boiled for 4 hours, during which a stream of nitrogen was passed. The solution was then evaporated under reduced pressure. The residual oil was decarbethoxylated by boiling its solution in acetic acid (10 c.c.) and concentrated hydrochloric acid (8·5 c.c.) for 40 minutes. The solution was again evaporated under reduced pressure and the residue was warmed on the water-bath for several hours with 5% potassium hydroxide solution (40 c.c.). Finally, the product was extracted with ether and the crude unsaturated ketone recovered from the extract. This (0·3 g.) gave a *semicarbazone* which formed clusters of colourless needles (from ethanol), m. p. 240·5°, after becoming discoloured at 230° (Found : C, 63·4; H, 8·0; N, 20·2. $C_{11}H_{17}ON_3$ requires C, 63·8; H, 8·2; N, 20·3%).

For hydrogenation, a solution of the crude unsaturated ketone (0·6 g.) in ethanol (30 c.c.) was shaken with hydrogen and palladium-black (0·1 g.) until hydrogen was no longer absorbed. The resulting saturated ketone (probably XII) gave a semicarbazone which crystallised from ethanol in colourless needles, m. p. 210—211°. The mixed m. p. with a specimen of the semicarbazone, m. p. 222—223°, of *cis*-8-methyl-1-hydrindanone (XI), prepared by degradation of *cis*-9-methyl-1-decalone, was 200—202°, after previous sintering.

UNIVERSITY OF GLASGOW. [*Received, March 5th*, 1947.]

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41. *Azulenes. Part II. Exploration of New Synthetic Routes.*

By J. W. COOK, R. PHILIP, and A. R. SOMERVILLE.

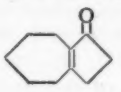
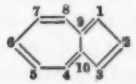
Naturally occurring hydroazulene derivatives have not yet been prepared synthetically, although the blue azulenes which they yield on dehydrogenation have been synthesised. In an endeavour to synthesise the optically inactive tetrahydride (VIII) which is formed by reduction of optically active β-vetivone, the hydrindanone derivative (IV) has been prepared by a simplified route and converted, in three stages, into the *dicarboxylic acid* (VII). Distillation of the thorium salt of this acid gave a product which may have been (VIII), but the amount was insufficient for characterisation.

By a five-stage process azulene (II) has been synthesised from suberone, which is readily prepared from *cyclo*hexanone. By a similar method 2 : 3-benz-1-suberone has been converted into 1-*keto*-4 : 5-*benz*-$\Delta^{4:9}$-*hexahydroazulene* (XIII), from which it is hoped to synthesise 4 : 5-benzazulene and some of its derivatives.

IN Part I (*J.*, 1942, 559) Coats and Cook described a synthesis of 4 : 7-dimethyl-2-*iso*propylhydrindan-5-one (IV). This was converted in small yield into vetivazulene by ring-enlargement with diazomethane, followed by dehydrogenation with selenium. We have now examined the possibility of using the same ketone (IV) as an intermediate in the synthesis of tetrahydro-β-vetivone (VIII), an internally compensated optically inactive ketone which Pfau and Plattner (*Helv. Chim. Acta*, 1939, **22**, 640) obtained by reduction of the optically active natural sesquiterpene ketone, β-vetivone (compare *idem*, *ibid.*, 1940, **23**, 768). Circumstances caused

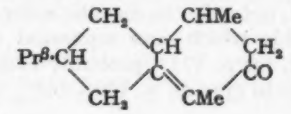
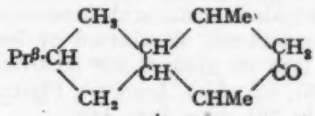
interruption of our work a year ago, and we wish now to record our experiments in view of the use by Plattner and Studer (*ibid.*, 1946, **29**, 1432) of a somewhat similar series of reactions for the synthesis of 6-methylazulene (see also Šorm and Fajkoš, *Coll. Czech. Chem. Comm.*, 1947, **12**, 81; Šorm, *ibid.*, p. 251).

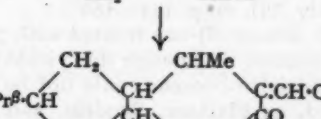
We have also been interested in devising a simple synthetic route to azulene derivatives to facilitate more detailed study of the chemistry of this interesting type of quasi-aromatic ring system. A way to this objective seemed to be provided by an adaptation of the work of Johnson and his collaborators (*J. Amer. Chem. Soc.*, 1945, **67**, 1357, 1360, 1366) who improved the Stobbe condensation of ethyl succinate with cyclic ketones, and showed how the condensation products could be transformed into condensed-ring *cyclo*pentane derivatives. We found that the product of condensation of suberone with ethyl succinate was readily converted into a dicyclic ketone (I) which was reduced in two stages to decahydroazulene, from which azulene (II) was obtained in small yield by dehydrogenation with selenium. In this work we have been largely anticipated by Plattner and Büchi (*Helv. Chim. Acta*, 1946, **29**, 1608) who prepared the dicyclic ketone (I) by the same method which we used, and converted it into 1-methylazulene. We therefore record our own experiments, insofar as they supplement those of the Swiss authors.

(I.)  (II.) 

Coats and Cook (*loc. cit.*) obtained 4 : 7-dimethyl-2-*iso*propylhydrindan-5-one (IV) by hydrogenation of the crude unsaturated ketone (III) which we have now characterised by the preparation of its *oxime* and *semicarbazone*. An important intermediate in this synthesis was *p-iso*propylphenol which was prepared from benzene by a laborious series of reactions. We have simplified the preparation of this phenol by modifying the method of von Braun (*Annalen*, 1929, **472**, 67; cf. U.S.PP. 1,788,847, 1,782,621; D.R.-PP. 467,640, 510,442), who found that both *p-iso*propylphenol and 4-*iso*propyl*cyclo*hexanol could be obtained by hydrogenolysis of the 2 : 2-di-(*p*-hydroxyphenyl)propane which arises from the condensation of phenol with acetone. In our experience copper chromite at 220—230° proved to be the most satisfactory catalyst for hydrogenolysis, by which *p-iso*propylphenol was obtained in 35% yield. This was then hydrogenated by Raney nickel to 4-*iso*propyl*cyclo*hexanol, from which the ketone (IV) was obtained by the procedure of Coats and Cook.

In conformity with the findings of these authors, the unsaturated ketone (III) was hydrogenated by palladium-black at room temperature to give a stereoisomeric mixture of saturated ketones from which a pure constituent giving a semicarbazone, m. p. 204°, was readily and consistently isolated in relatively small yield. Hydrogenation was very slow, and in order to accelerate the reaction the main batch of unsaturated ketone was treated with hydrogen under pressure at 50° in presence of palladised strontium carbonate. This modification of the conditions had a profound influence on the composition of the resulting mixture. The semicarbazone of m. p. 204° was not isolated; there was obtained instead a semicarbazone mixture from which was isolated by recrystallisation only a small amount of well crystallised, apparently homogeneous

(III.)  (IV.) 



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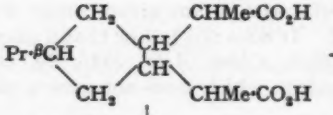
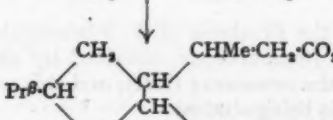
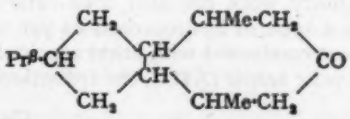
(VI.) 



(VII.)

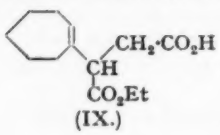
(VIII.) 

material, m. p. 175°. The same *semicarbazone*, in an impure state (m. p. 168°), had been obtained by Coats and Cook by the action of diazomethane on the ketone which forms the

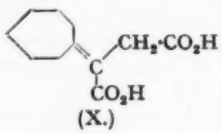
semicarbazone, m. p. 204°. The two ketones corresponding with these semicarbazones are clearly stereoisomeric, and it was the failure to obtain a satisfactory quantity of stereochemically homogeneous ketone (IV) which has frustrated the complete attainment of the objective of this work, namely, synthesis of a compound of the structure (VIII).

A possible method of ring-enlargement of the six-membered ring in (IV) was the action of nitrous acid on the amine which should be obtainable by reduction of the cyanohydrin of (IV). On account of the structural ambiguity of the perhydroazulene derivative which should be formed this method was not adopted, but such a method has in fact been used as a synthetic route to azulene derivatives (compare Arnold, *Ber.*, 1943, **76**, 777). After some exploratory experiments in regard to other methods, it was decided to convert the ketone (IV) into the dicarboxylic acid (VI), through the hydroxymethylene-ketone (V). The ketone (IV*a*), regenerated from the semicarbazone, m. p. 204°, reacted with sodium and ethyl formate to give a golden-yellow, acid, liquid hydroxymethylene ketone (V), together with a colourless neutral crystalline *isomeride*, m. p. 70°, which appeared to be the tautomeric formyl ketone. This colourless solid gave an intense violet colour with ferric chloride but formed a *disemicarbazone*. The same neutral product, together with a liquid hydroxymethylene compound, was obtained by analogous treatment of the ketone (IV*b*) regenerated from the semicarbazone, m. p. 175°. Permanganate oxidation of the hydroxymethylene ketone (V), obtained from the ketone (IV*a*), gave 1-iso*propyl*cyclo*pentane*-3 : 4-*bis*-(α-*propionic acid*) (VI), m. p. 154—156°. A satisfactory product could not be obtained by similar oxidation of the hydroxymethylene derivative of the isomeric ketone (IV*b*).

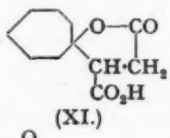
By the Arndt–Eistert method adipic acid has been converted into suberic acid and sebacic acid into decane-1 : 10-dicarboxylic acid (Walker, *J.*, 1940, 1304). When the dicarboxylic acid (VI) was submitted to this technique it was smoothly converted into 1-iso*propyl*cyclo*pentane*-3 : 4-*bis*-(β-*butyric acid*) (VII). By distillation of the thorium salt of this homologous acid there was formed a pleasant-smelling liquid, which gave a red precipitate with 2 : 4-dinitrophenylhydrazine. This liquid may have been the desired ketone (VIII), but the amount of material available was insufficient for characterisation.



(IX.)

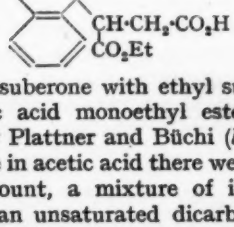


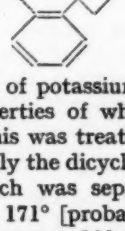
(X.)



(XI.)

(XII.)





(XIII.)

Condensation of suberone with ethyl succinate by means of potassium *tert.*-butoxide gave *cyclo*heptenylsuccinic acid monoethyl ester (IX), the properties of which agreed with the description given by Plattner and Büchi (*loc. cit.*). When this was treated with zinc chloride and acetic anhydride in acetic acid there were obtained, not only the dicyclic ketone (I) but also, in much larger amount, a mixture of isomeric acids which was separated by fractional crystallisation into an unsaturated dicarboxylic acid, m. p. 171° [probably *cyclo*heptylidene-succinic acid (X), for which, however, Plattner and Büchi give m. p. 160—163°], and a *lactonic acid* (presumably XI), m. p. 184—186°.

The dicyclic ketone (I) was treated with phenylmagnesium bromide, and the crude product heated with selenium. Although this yielded a material with a blue-green colour, a crystalline complex with *s*-trinitrobenzene could not be isolated. It does not follow that a phenylazulene was not formed, as Plattner, Sandrin, and Wyss (*Helv. Chim. Acta*, 1946, **29**, 1604) found that 1-phenylazulene easily isomerises to 2-phenylazulene which does not give a picrate or a trinitrobenzene complex.

Preliminary work has also been carried out on the synthesis of 4 : 5-benzazulene, which represents a type of hydrocarbon as yet unknown. Benzsuberone, obtained by an improved method, was condensed with ethyl succinate to give the *mono-ester* (XII), and this was cyclised to the tricyclic *ketone* (XIII), the reduction of which is being studied.

Experimental.

p-iso*Propylphenol*.—2 : 2-Di-(*p*-hydroxyphenyl)propane was prepared from phenol, acetone, and fuming hydrochloric acid as described by Zincke (*Annalen*, 1905, **343**, 85). This method was found

superior to that of von Braun (*loc. cit.*). For hydrogenolysis, a mixture of the crude diphenol (380 g.) and the copper chromite catalyst (*Org. Synth.*, Coll. Vol. II, 142) (38 g.) was agitated with hydrogen for 5 hours in a stainless-steel autoclave heated at 220—230°. The initial pressure was 180 atm., and during the course of the reaction some 70 l. of hydrogen were absorbed. The viscous product was distilled into two fractions: (i) b. p. 88—100°/15 mm. (130 g.), (ii) b. p. 100—125°/15 mm. (100 g.). Fraction (ii) crystallised and gave colourless needles, m. p. 62—63°, of *p-iso*propylphenol. This was hydrogenated over Raney nickel as described by Coats and Cook (*loc. cit.*) and gave a mixture of stereoisomeric 4-*iso*propyl*cyclo*hexanols, the heterogeneous nature of which was shown by conversion into a mixture of acid phthalates, m. p. 90—98°. 1 Kg. of *iso*propyl*cyclo*hexanol was prepared in this way.

5-*Keto*-4 : 7-*dimethyl*-2-iso*propyl*-$\Delta^{4(9)}$-*tetrahydroindane* (III).—Very slow addition of the mixture of *iso*propyl*cyclo*hexanols to 50% nitric acid catalysed by ammonium vanadate (Coats and Cook, *loc. cit.*) gave *β-iso*propyladipic acid (80% yield), which crystallised when the reaction mixture was cooled in a refrigerator. This was esterified, the ester submitted to the Dieckmann reaction, and the product condensed with hex-2-en-4-one, all as described by Coats and Cook. In the preparation of hexenone from allyl bromide and propionitrile the best results were obtained by using zinc powder freshly prepared by milling pure zinc rods. A trace of pyridine was used to initiate the reaction. The dicyclic keto-ester formed by this series of reactions was decarbethoxylated with boiling aqueous potassium hydroxide. The resulting ketone (III) reacted with semicarbazide hydrochloride and potassium acetate in aqueous alcohol to give a *semicarbazone*, which crystallised from aqueous ethanol in colourless needles, m. p. 208—210° (Found: C, 68·5; H, 9·3; N, 16·1. $C_{15}H_{25}ON_3$ requires C, 68·4; H, 9·5; N, 16·0%). The *oxime*, obtained from the crude ketone by treatment with hydroxylamine hydrochloride in boiling pyridine solution, formed clusters of small colourless needles (from ethanol), m. p. 172·5—173·5° (Found: C, 76·2; H, 10·2; N, 6·45. $C_{14}H_{23}ON$ requires C, 76·0; H, 10·4; N, 6·3%).

The distilled ketone (b. p. 88°/0·15 mm.), obtained by steam distillation of the pure semicarbazone with oxalic acid, was hydrogenated in ethanolic solution by means of palladium-black. In spite of the homogeneity of the unsaturated ketone (III), the hydrogenation product was a mixture of stereoisomerides (IV), for the semicarbazone prepared from it had m. p. *ca.* 170°, raised to 201° by 3 recrystallisations from ethanol. The purified semicarbazone was identical with the compound similarly prepared by Coats and Cook from the crude unsaturated ketone. By fractional crystallisation of the material from the liquors of the semicarbazone, there was obtained a fraction, m. p. 156—164° depressed to 150° by admixture with the semicarbazone, m. p. 201°. It is, of course, possible for 4 stereoisomerides to arise by hydrogenation of the ethylenic bond in (III). As the use of the pure unsaturated ketone offered no advantage over that of the crude material, the latter was used in subsequent work.

When working with a larger batch, a solution of the unsaturated ketone (III) (50 g.) in ethanol (500 c.c.) was agitated for 6 hours with hydrogen and palladised strontium carbonate (20 g.) at 50° and 110 atm. The filtered solution gave a resinous mixture of semicarbazones from which was eventually obtained by fractional crystallisation from ethanol a crystalline semicarbazone, m. p. 162—164° (8 g.), not depressed by admixture with the semicarbazone, m. p. 167—168°, obtained by Coats and Cook from the ketone recovered from the action of diazomethane on the saturated ketone (IV*a*) which gives a semicarbazone, m. p. 204°. Further crystallisation from ethanol gave colourless leaflets of the *semicarbazone*, m. p. 175—176° (Found: C, 67·7; H, 10·4. $C_{15}H_{27}ON_3$ requires C, 67·9; H, 10·2%). The *ketone* (IV*b*) recovered from this by steam distillation with 20% sulphuric acid was distilled in an air-bath at 85°/0·3 mm. and formed a colourless liquid (Found: C, 80·8; H, 11·4. $C_{14}H_{24}O$ requires C, 80·8; H, 11·5%), which reacted with semicarbazide to form the semicarbazone from which it was obtained.

Oxidation of the mixed ketones (IV) with hydrogen peroxide and vanadium pentoxide (Treibs, *Ber.*, 1939, **72**, 1194) gave no useful result. Oxidation of the pure ketone (IV*a*) (1 g.) with amyl nitrite (0·6 g.) and concentrated hydrochloric acid (0·5 c.c.) for 9 hours gave the keto-acid, m.p. 71—72°, obtained by Coats and Cook by oxidation of the same ketone with chromic acid (the earlier sample had m. p. 64—65°). (Found: C, 69·9; H, 10·0. Calc. for $C_{14}H_{24}O_3$: C, 69·9; H, 10·1%).

4 : 7-*Dimethyl*-6-*hydroxymethylene*-2-iso*propylhydrindan*-5-*one* (V).—(*a*) Ethyl formate (5·5 c.c.) was added to a suspension of atomised sodium (1 g.) in the pure ketone (IV*a*) (1 g.) and anhydrous ether (25 c.c.). A vigorous reaction ensued and the colour became yellow and then red. After 24 hours at room temperature, the mixture was poured into ice-water (300 c.c.) and extracted with ether. A white solid which separated at the interface was collected and added to a further quantity obtained by distillation of the ethereal extract. This compound, probably 6-*formyl*-4 : 7-*dimethyl*-2-iso*propylhydrindan*-5-*one*, crystallised from acetic acid in colourless rhombic plates, m. p. 69—70° (Found: C, 76·7; H, 9·8. $C_{15}H_{24}O_2$ requires C, 76·3; H, 10·2%). It gave an intense violet colour with ferric chloride, and formed a *disemicarbazone*, m. p. 206—208° (Found: C, 58·4; H, 8·5. $C_{17}H_{30}O_2N_6$ requires C, 58·3; H, 8·6%). The alkaline solution containing the hydroxymethylene-ketone was acidified with hydrochloric acid and then extracted with ether. Distillation of the dried extract gave a golden-yellow viscous liquid (0·6 g.), b. p. 98—105°/0·2 mm. (bath temp.). This hydroxymethylene-ketone (V*a*) gave an intense violet colour with ferric chloride.

(*b*) A similar experiment with the stereoisomeric ketone (IV*b*) gave the corresponding yellow viscous hydroxymethylene-ketone (V*b*) and also a small amount of the solid formyl compound, m. p. 69—70°, described under (*a*).

It was found disadvantageous to carry out these condensations with large batches of ketone.

1-iso*Propyl*cyclo*pentane*-3 : 4-*bis*-(*α-propionic Acid*).—(*a*) A solution of the hydroxymethylene ketone (V*a*) (0·5 g.) in 10% sodium hydroxide (1·5 c.c.) was treated dropwise at 0° with an ice-cold solution of potassium permanganate (1 g. in 38 c.c.). After several hours at 0° the permanganate was completely reduced and the filtered solution was acidified and extracted with ether. The dried ethereal extract was evaporated and gave a gum which partly crystallised in a vacuum desiccator. The residual oil was removed by extraction with hexane and the undissolved solid was crystallised from water and then hexane. The *dipropionic acid* (VI) formed colourless cubes (0·2 g.), m. p. 154—156° (Found: C, 65·6; H, 9·0. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%). The *di*-p-*phenylphenacyl* ester formed tufts of

colourless needles (from ethanol), m. p. 153—153·5° (Found: C, 78·0; H, 7·05. $C_{42}H_{44}O_6$ requires C, 78·2; H, 6·8%).

(*b*) Similar oxidation of the isomeric hydroxymethylene-ketone (V*b*) gave a resinous acid which could not be crystallised. Its *p*-phenylphenacyl ester was obtained as colourless microscopic needles, m. p. 132—146°, very slightly depressed by admixture with the isomeric ester described under (*a*).

1-iso*Propyl*cyclo*pentane*-3 : 4-*bis*-(*β*-*butyric Acid*).—The acid (VI), m. p. 154°(0·75 g.), was added to thionyl chloride (2 c.c.) at 0°, and the mixture kept for 20 hours. The excess of thionyl chloride was distilled under reduced pressure, and this process was twice repeated after addition, first of ether and then of benzene. A solution of the residual viscous liquid in ether (12 c.c.) was added dropwise at 0° to ethereal diazomethane (from 9 g. of nitrosomethylurea). After being kept overnight the solution was concentrated under diminished pressure and the lemon-yellow solid (0·3 g.) which separated was collected. This *aa'-bisdiazoacetyl*-3 : 4-*diethyl*-1-iso*propyl*cyclo*pentane* crystallised from hexane in yellowish microscopic needles, m. p. 111—111·5° (Found: C, 63·8; H, 7·7. $C_{16}H_{24}O_2N_4$ requires C, 63·2; H, 7·9%).

A solution of this bisdiazo-ketone (0·3 g.) in dioxan (20 c.c.) was heated on the water-bath and treated with 20% aqueous ammonia (1·5 c.c.) and 10% silver nitrate solution (0·3 c.c.). After being heated for 1½ hours the solution was filtered, and the filtrate concentrated to 10 c.c. and again filtered. Evaporation to dryness gave a gum which solidified when rubbed with hexane. This product, presumably a diamide, was hydrolysed by boiling with methanolic potassium hydroxide (0·4 g. in 6 c.c.) until ammonia was no longer liberated (several hours). The acid (0·12 g.) recovered after concentration and acidification was twice recrystallised from aqueous acetic acid. 1-iso*Propyl*cyclo*pentane*-3 : 4-*bis*-(*β*-*butyric acid*) (VII) formed somewhat discoloured fine needles, m. p. 172—173° (Found: C, 68·1; H, 10·2. $C_{16}H_{28}O_4$ requires, C, 67·6; H, 9·9%).

γ-iso*Propylsuberic Acid*.—This was prepared from *β*-*iso*propyladipic acid in order to gain experience of the Arndt–Eistert reaction with this type of compound. The *iso*propyladipic acid was converted into its chloride and this treated with diazomethane, to give the bis-diazoacetyl compound, which could not be crystallised. It was treated with ammonia and silver nitrate in aqueous dioxan, and the resulting crude amide was hydrolysed with aqueous potash, all these operations being carried out essentially as in the example described above. *γ*-iso*Propylsuberic acid* crystallised from hexane in colourless needles, m. p. 69·5—71° (Found: C, 60·9; H, 9·0. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·25%). By heating its thorium salt at 300—350° under reduced pressure there was formed a mobile liquid distillate having an odour of violets. It gave a semicarbazone, but with the small quantity of material available this could not be obtained analytically pure.

α-(2-*Keto*-4-iso*propyl*cyclo*pentyl*)*propionic Acid*.—This was prepared in connection with an alternative scheme for the synthesis of the dicarboxylic acid (VI), but in view of the small yield obtained the scheme was not pursued further. Ethyl 4-*iso*propyl*cyclo*pentanone-2-carboxylate (Coats and Cook, *loc. cit.*) (10 g.) was added to a suspension of powdered sodium (1·2 g.) in benzene (40 c.c.) and the mixture was heated under reflux for 2 hours. To the cooled suspension of sodio-compound thus formed was added ethyl *α*-bromopropionate (10 g.). The mixture was heated on the steam-bath for 6 hours, cooled, poured into water, and extracted with ether; the benzene–ether layer was dried (Na_2SO_4) and distilled. The principal fraction (8·8 g.) formed a colourless liquid, b. p. 140—180°/10 mm. This crude keto-ester was hydrolysed by boiling its suspension in concentrated hydrochloric acid (60 c.c.) for 6 hours. The crude acidic product formed a resin which solidified when treated with light petroleum. After three recrystallisations from hexane *α*-(2-*keto*-4-iso*propyl*cyclo*pentyl*)*propionic acid* formed small colourless needles, m. p. 109—110° (Found: C, 66·6; H, 9·3. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%). The ethyl ester, b. p. 145—150°/15 mm., prepared from the crude acid, gave a *semicarbazone* which crystallised from aqueous methanol in long flat needles, m. p. 164—166·5° (Found: C, 59·6; H, 8·8; N, 14·8. $C_{14}H_{23}O_3N_3$ requires C, 59·3; H, 8·9; N, 14·8%).

Cyclisation of Monoethyl Ester of cyclo*Heptenylsuccinic Acid* (IX).—The crude ester was obtained in 80% yield by condensation of suberone with ethyl succinate, using essentially the conditions described by Plattner and Büchi (*loc. cit.*). Our purified material had m. p. 68—70° (Found: C, 65·1; H, 8·2. Calc. for $C_{13}H_{20}O_4$: C, 65·0; H, 8·4%). Plattner and Büchi give m. p. 68·5—69°. A solution of the crude half-ester (13·6 g.) in acetic anhydride (155 c.c.) and acetic acid (80 c.c.) containing fused zinc chloride (20 mg. per c.c.) was boiled under reflux for 3½ hours, during which a slow stream of nitrogen was passed into the reaction flask. Water (155 c.c.) and concentrated hydrochloric acid (60 c.c.) were then added and boiling continued for ½ hour, to hydrolyse the intermediate keto-ester. The solvents were distilled off under reduced pressure, and the residue heated on the steam-bath for ½ hour with 5% potassium hydroxide solution (200 c.c.). Extraction with ether then removed the dicyclic ketone (I), which, after purification through the semicarbazone, m. p. 235—236° (Plattner and Büchi give m. p. 238°), formed a colourless liquid, b. p. 58—60°/0·1 mm.; $n_D^{17\cdot5}$ 1·5275 (Found: C, 79·9; H, 9·2. Calc. for $C_{10}H_{14}O$: C, 80·0; H, 9·4%) (25% yield).

Acidification of the alkaline solution from which the ketone had been extracted precipitated a mixture of acids (28·2 g. obtained from 57·5 g. of the half-ester) which was separated by fractional crystallisation from aqueous acetic acid into two components. One of these formed stout colourless needles, m. p. 171°, and rapidly reduced potassium permanganate solution (Found: C, 62·3; H, 7·2; equiv., by titration with alcoholic potash, 106·5. Calc. for $C_{11}H_{16}O_4$: C, 62·3; H, 7·6%; equiv., 106). This is regarded as *cyclo*heptylidenesuccinic acid (X), obtained by Plattner and Büchi by direct hydrolysis of the half-ester (IX). The second acid, which was stable to permanganate, formed small colourless plates, m. p. 184—186° (Found: C, 62·3; H, 7·4; equiv., by direct titration, 211; by solution in alkali and back-titration, 97. $C_{11}H_{16}O_4$ requires, C, 62·3; H, 7·6%; equiv., 212). These data support the view that the compound is the *lactonic acid* (XI). It was recovered unchanged from an attempt to convert it into the dicyclic ketone (I) by boiling acetic acid–acetic anhydride containing zinc chloride. Attempts to cyclise the unsaturated acid (X) by means of an internal Friedel–Crafts reaction or of the half-ester (IX) by treatment with anhydrous hydrogen fluoride also failed.

The work of Johnson *et al.* (*J. Amer. Chem. Soc.*, 1945, **67**, 2274) suggested that better results might be obtained by condensing ethyl succinate with α-cyanosuberone rather than suberone itself. By a similar reaction Johnson synthesised a condensed 5-membered ring in one operation. For the preparation of α-cyanosuberone (Ziegler *et al.*, *Annalen*, 1933, **504**, 117), hydroxymethylenesuberone (Wallach and Steindorff, *ibid.*, 1903, **329**, 128) was treated with hydroxylamine followed by sodium methoxide, as described by Johnson and Shelberg (*J. Amer. Chem. Soc.*, 1945, **67**, 1745) for a similar case. A by-product of the reaction was 3 : 4-cyclo*heptenoisooxazole*, which was extracted from the mother-liquors of the crude cyanosuberone by means of ethanolic mercuric chloride. The mercurichloride was decomposed with alkali, and the *iso*oxazole isolated by steam distillation. It formed a colourless liquid, b. p. 59—52°/0·2 mm. (Found : C, 69·5; H, 7·6; N, 10·0. $C_8H_{11}ON$ requires C, 70·1; H, 8·0; N, 10·2%). Condensation of α-cyanosuberone with ethyl succinate, in presence of potassium *tert.*-butoxide, gave no ketonic product.

Azulene.—Hydrogenation of 1-keto-$\Delta^{9:10}$-octahydroazulene (I) was effected in ethanolic solution by Adams's platinum catalyst or, more rapidly, by palladised strontium carbonate. The resulting 1-ketodecahydroazulene gave a homogeneous *semicarbazone*, m. p. 229—230° (decomp.) (Found : C, 63·3; H, 8·9; N, 20·0. $C_{11}H_{19}ON_3$ requires C, 63·2; H, 9·1; N, 20·1%). Reduction of the saturated ketone with amalgamated zinc and hydrochloric acid containing a little acetic acid gave, after 30 hours, a 60% yield of the saturated hydrocarbon, b. p. 192° (Plattner, Fürst, and Jirasek, *Helv. Chim. Acta*, 1946, **29**, 730, give b. p. 80°/11 mm.). This hydrocarbon was resistant to dehydrogenation which was, however, achieved by heating with selenium (2 parts) at 360° for 4 days in a long-necked flask with an internal condenser. In the later stages the temperature was raised to above 400°. The deep blue solution of the product in light petroleum was extracted with phosphoric acid (*d* 1·75), and the acid solution diluted and extracted with ether. On evaporation of the ether, azulene remained as a blue solid, and was purified through its *s*-trinitrobenzene complex (55 mg. from 1·1 g. of decahydroazulene), m. p. 165—167° (lit., 166·5—167·5°) (Found, N, 11·9. Calc. for $C_{16}H_{11}O_6N_3$: N, 12·3%). A solution of this complex in hexane was passed through a column of alumina, and gave blue crystals of azulene, micro-m. p. 85—89°.

δ-*Phenylvaleric Acid.*—This was obtained in 63% yield from cinnamaldehyde by the following procedure, which represents a vast improvement on the yields claimed by previous workers (compare Kadesch, *J. Amer. Chem. Soc.*, 1944, **66**, 1212) : Cinnamaldehyde (100 g.), malonic acid (80 g.), and quinoline (98 g.) were warmed together on the water-bath until a clear red solution was formed. Piperidine (2 c.c.) was then added, and the solution was cooled and kept in the dark for 10 days. The solid mass was treated with excess of sodium hydroxide solution, the quinoline was extracted with ether, and the alkaline solution was acidified. This precipitated cinnamylidenemalonic acid (153 g.), which was reduced in alkaline solution to γ-phenylpropylmalonic acid by means of a nickel–aluminium alloy (cf. Schwenck, Papa, Whitman, and Ginsberg, *J. Org. Chem.*, 1942, **7**, 587; 1944, **9**, 1, 175). For this purpose, Raney nickel alloy (135 g.) was added during 2 hours to a stirred, almost boiling, solution of crude cinnamylidenemalonic acid (137 g.) in sodium hydroxide (230 g. in 1500 c.c. of water). To minimise frothing, a little *sec.*-octyl alcohol was added. The mixture was stirred at 90° for another hour, filtered, and the filtrate slowly run into a hot solution of sulphuric acid (450 c.c. of concentrated acid in 1 l. of water). The main bulk of the precipitated oil was not purified, but was separated and then heated under reduced pressure at 140—180° for 2 hours, in order to decarboxylate the phenylpropylmalonic acid. The resulting δ-phenylvaleric acid (75·5 g.) required very little purification.

Cyclisation of this acid to 2 : 3-benzsuberone was effected in 90% yield by the excellent method of Plattner (*Helv. Chim. Acta*, 1944, **27**, 804), but no reaction occurred when the acid was treated with anhydrous hydrogen fluoride.

1-*Keto*-4 : 5-*benz*-$\Delta^{4:9}$-*hexahydroazulene* (XIII).—Benzsuberone (5 g.) was condensed with ethyl succinate (8·25 g.) by means of potassium *tert.*-butoxide (1·5 g. of potassium in 30 c.c. of *tert.*-butyl alcohol) as in the case of suberone. The crude half-ester (XII) gave crystals, m. p. 170—173°, by sublimation at 0·2 mm., but the analysis figures of these were not satisfactory. This half-ester (5·2 g.) was treated in the usual manner with acetic anhydride (52 c.c.) and acetic acid (26 c.c.), containing zinc chloride. In addition to acidic products which were not investigated, there was formed a neutral oil (1 g.) which was separated by distillation into (*a*) a fraction, b. p. 125—130°/0·4 mm., and (*b*) a residue which sublimed at 155—160°/0·4 mm. Fraction (*b*) crystallised from ethanol in colourless prisms, m. p. 199—201° (Found : C, 75·4; H, 6·0%). This material, which gave a 2 : 4-dinitrophenylhydrazone only on long standing, was not further examined. Fraction (*a*) was the desired *ketone* (XIII), and crystallised from methanol in long colourless needles, m. p. 60—62° (Found : C, 84·9; H, 7·0. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%); it gave a *semicarbazone*, which formed clusters of colourless needles (from ethanol), m. p. 236° (decomp.) after sintering (Found : C, 69·7; H, 6·5; N, 16·6. $C_{15}H_{17}ON_3$ requires C, 70·6; H, 6·7; N, 16·5%). Work on the conversion of this ketone into 4 : 5-benzazulene and its derivatives is being continued.

We are indebted to the Department of Scientific and Industrial Research for a Maintenance Allowance (to A. R. S.). The micro-analyses were carried out by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, March 5th*, 1947.]

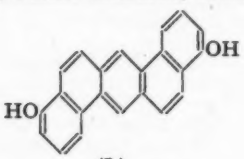
42. *Oxidation of Carcinogenic Hydrocarbons by Osmium Tetroxide.*

By J. W. Cook and (Miss) R. Schoental.

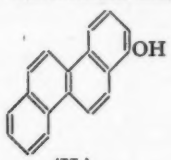
Ten polycyclic aromatic hydrocarbons, including some of the most potent cancer-producing compounds, have been oxidised by osmium tetroxide in benzene–pyridine to diols which undergo facile dehydration to hydroxy-derivatives of the original hydrocarbons. This process represents the closest parallel yet achieved to the biochemical oxidation of the hydrocarbons. The positions of attack are, however, different in the two processes. Thus, whereas metabolic oxidation of 1 : 2-benzanthracene leads to the 4′-hydroxy-derivative (III; R = H), chemical oxidation by the process now described leads to the 3-hydroxy-derivative (XI). Except in the case of chrysene the positions of the molecule which are attacked in metabolic oxidation and in oxidation with osmium tetroxide are both different from the positions which nearly all other chemical reagents show to be the most reactive positions.

In recent years considerable attention has been devoted to investigations of the metabolic transformations undergone in the animal body by polycyclic aromatic hydrocarbons, particularly those having cancer-producing activity. It has been supposed that these carcinogenic hydrocarbons, which on the whole are stable and rather inert, may exert their biological effects as a result of conversion into active metabolic products rather than by a direct action on the cells. The results of metabolic studies lend no support to this view, as the metabolic products, as far as they have been isolated, have proved to be either non-carcinogenic or less active than the hydrocarbons from which they are derived. The metabolic processes seem rather to represent a means of detoxification and elimination of the biologically active compounds.

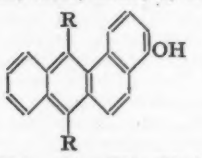
A common method of biochemical study has been to administer the hydrocarbon with the food of laboratory animals and to extract the excretion products from the urine or faeces, although other methods of administration have been used, and metabolic products have been detected in the tissues or body fluids. In many cases it has been found that elimination is preceded by hydroxylation, so that phenolic oxidation products are formed. Thus 1 : 2 : 5 : 6-dibenzanthracene is converted by rats and mice into the 4′ : 8′-dihdroxy-derivative (I) (Dobriner, Rhoads, and Lavin, *Cancer Research*, 1942, **2**, 95; Cason and Fieser, *J. Amer. Chem. Soc.*, 1940, **62**, 2681), and chrysene is converted into 3-hydroxychrysene (II) (Berenblum and Schoental, *Biochem. J.*, 1945, **39**, lxiv). There is strong evidence that the 4′-hydroxy-derivatives (III) are formed from 1 : 2-benzanthracene (Berenblum and Schoental, *Cancer Research*, 1943, **3**, 686) and 9 : 10-dimethyl-1 : 2-benzanthracene (Dickens and Weil-Malherbe, *22nd Annual Report of the British Empire Cancer Campaign*, 1945, p. 55), and that 3 : 4-benzpyrene (IV) is converted into a mixture of its 8- and 10-hydroxy-derivatives (cf. Berenblum, Crowfoot, Holiday, and Schoental, *Cancer Research*, 1943, **3**, 151; Berenblum and Schoental, *ibid.*, 1946, **6**, 699).



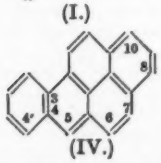
(I.)



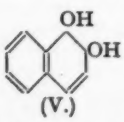
(II.)



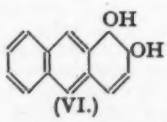
(III.) (R = H or Me.)



(IV.)



(V.)



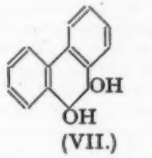
(VI.)

Oxidation of the hydrocarbon probably takes place through the intermediary of a diol formed by addition of hydroxyl groups to adjacent carbon atoms. Such diols (V and VI) have in fact been isolated from naphthalene (Young, *Canad. Chem.*, 1946, **30**, 124; *Biochem. J.*, 1947, **41**, 417) and anthracene (Boyland and Levi, *Biochem. J.*, 1935, **29**, 2679; Boyland and Shoppee, *J.*, 1947, 801). They are rapidly converted by treatment with dilute acid into α-naphthol and α-anthrol, respectively. Weigert and Mottram (*Cancer Research*, 1946, **6**, 109) have adduced spectroscopic evidence that there are intermediates in the biochemical oxidation of 3 : 4-benzpyrene to hydroxy-derivatives and have suggested that these intermediates are related to diols analogous to (V) and (VI).

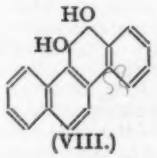
The positions in the molecules which are attacked in these biochemical oxidations are not those which have been revealed as the most reactive centres by purely chemical reagents. Thus, with 3 : 4-benzpyrene substitution almost invariably occurs in position 5, and this includes

oxidation by lead tetra-acetate which leads to the formation of the 5-acetoxy-derivative (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1938, **60**, 2542; 1939, **61**, 1565). Anthracene, 1 : 2-benzanthracene, and 1 : 2 : 5 : 6-dibenzanthracene are attacked at the reactive 9- and 10-positions of the anthracene system. This is reflected in substitution reactions, in oxidation to the quinones, in photo-oxidation to transannular peroxides, and in Diels–Alder addition of maleic anhydride and similar reagents. In general this is true also of homologues, although substitution may sometimes occur in reactive positions of side chains as in the lead tretra-acetate oxidation of 9 : 10-dimethyl-1 : 2-benzanthracene (cf. III) to the ωω′-diacetoxy-derivative (Badger and Cook, *J.*, 1939, 802). Eckhardt (*Ber.*, 1940 **73**, 13) compared the rates of oxidation of several polycyclic aromatic hydrocarbons by perbenzoic acid, but did not isolate the products.

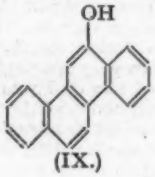
In view of these striking contrasts between the positions attacked in biochemical and in chemical oxidation it seemed of interest to examine the oxidation of polycyclic aromatic hydrocarbons by osmium tetroxide. An improvement on the original procedure of Criegee (*Annalen*, 1936, **522**, 75) was introduced by Criegee, Marchand, and Wannowius (*ibid.*, 1942, **550**, 99), who showed that if ethylenic compounds were treated with osmium tetroxide in presence of tertiary bases, especially pyridine, there were formed bright-coloured stable crystalline complexes having the character of esters of osmic acid. Such a complex was obtained by these authors from phenanthrene also, and underwent hydrolytic decomposition to 9 : 10-dihydroxy-9 : 10-dihydrophenanthrene (VII). We have found that this is a general reaction for polycyclic hydrocarbons containing a phenanthrene system. Chrysene was converted into 1 : 2-*dihydroxy*-1 : 2-*dihydrochrysene* (VIII) which was dehydrated by dilute acid to 2-chrysenol (IX); pyrene was converted into 1 : 2-*dihydroxy*-1 : 2-*dihydropyrene*, dehydrated to 1-pyrenol; and 1 : 2-benzanthracene was converted into 3 : 4-*dihydroxy*-3 : 4-*dihydro*-1 : 2-*benzanthracene* (X), dehydrated to 3-hydroxy-1 : 2-benzanthracene (XI). The last-named compound was identified by comparison of its methyl ether with synthetic 3-methoxy-1 : 2-benzanthracene prepared by the method of Fieser, Hershberg, Long, and Newman (*J. Amer. Chem. Soc.*, 1937, **59**, 475). Moreover, the diol (X) was oxidised by chromic acid to the known 1 : 2-benz-3 : 4-anthraquinone (Fieser and Dietz, *J. Amer. Chem. Soc.*, 1929, **51**, 3141).



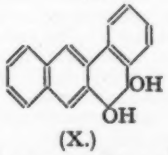
(VII.)



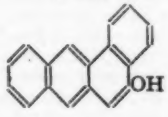
(VIII.)



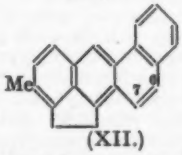
(IX.)



(X.)



(XI.)



(XII.)

Similar oxidation to *diols* by osmium tetroxide in benzene–pyridine followed by hydrolysis took place with 1′-methyl-, 9 : 10-dimethyl-, 5 : 9 : 10-trimethyl-, and 5 : 6 : 9 : 10-tetramethyl-1 : 2-benzanthracene, 1 : 2 : 5 : 6-dibenzanthracene, and 20-methylcholanthrene (XII). The diols were characterised by their *diacetates* and they were all readily dehydrated to phenolic hydroxy-compounds from which homogeneous *methyl ethers* were obtained by methylation. These diols and their dehydration products may be assumed by analogy to have structures corresponding with (X) and (XI), although the positions of the substituents have not been verified experimentally. It is reasonably certain, from the work of Criegee and his collaborators (*loc. cit.*) (cf. Böeseken, *Rec. Trav. chim.*, 1922, **41**, 199) that all the diols have the *cis*-configuration. It is of interest that catalytic hydrogenation of 20-methylcholanthrene (XII) leads in part to addition of hydrogen at the positions (6, 7) which are believed to be concerned in the addition of osmium tetroxide, although this is not so with 1 : 2-benzanthracene (Fieser and Hershberg, *J. Amer. Chem. Soc.*, 1937, **59**, 2502; 1938, **60**, 940).

3 : 4-Benzpyrene (IV) was also rapidly hydroxylated under the conditions used in these oxidations. The diol so formed was sensitive to atmospheric oxidation and could not be obtained completely pure, but it formed a well-crystallised *diacetate*. Dehydration by dilute acid gave a mixture of phenols from which, after methylation, two *methoxybenzpyrenes* were isolated. They were separated by fractional crystallisation of their picrates, combined with chromatographic purification. These two methoxybenzpyrenes differed from the known methoxybenz-

pyrenes (with substituents at positions 5, 10, and 4') and were probably the 6- and 7-methoxy-compounds, the synthesis of which is being attempted.

The diols formed by hydroxylation of these polycyclic hydrocarbons by means of osmium tetroxide were obtained in good yield, and apart from the isolation of a small amount of 1 : 2 : 5 : 6-dibenz-3 : 4-anthraquinone as a by-product in the chromic acid oxidation of 1 : 2 : 5 : 6-dibenzanthracene (Cook, *J.*, **1933**, 1592), their formation represents the first successful chemical oxidation of benzanthracene hydrocarbons in positions other than the reactive *meso*-positions of the anthracene system which they contain. The process obviously offers a very close parallel to the biochemical oxidation of the hydrocarbons, although the points of attack in the molecule are different. It may well be that the biochemical oxidation involves a similar formation of a metallic complex involving an oxidising enzyme system, but it remains a matter of conjecture why such a process should take place at some of the less reactive centres in the molecule. Possibly some form of steric influence is operative.

If osmium tetroxide oxidation could be effected in the simpler cases of naphthalene and anthracene, the metabolic diols (V and VI) could perhaps be obtained artificially. These hydrocarbons do indeed form coloured crystalline complexes with pyridine–osmium tetroxide, and the products which these yield on hydrolysis are being investigated.

Experimental.

Preparation of the Osmic Ester–Pyridine Complexes.—A solution (or suspension) of the hydrocarbon (0·0025 mole) in pure dry benzene (15 c.c.) was treated with osmium tetroxide (0·0025 mole) and purified pyridine (0·005 mole). The colour slowly deepened and the dark brown microcrystalline complex was deposited. With 3 : 4-benzpyrene and 1 : 2-benzanthracene and its homologues reaction was complete in 24 to 48 hours at room temperature, after which the decanted clear solution deposited no further precipitate. With less reactive or less soluble hydrocarbons (*e.g.*, anthracene, 1 : 2 : 5 : 6-dibenzanthracene) the reaction required several days or even weeks, at room temperature. With chrysene the reaction was completed in a week at 35°.

Formation of the Diols.—After complete separation from solution of the coloured complexes these were collected and dissolved in methylene chloride, and the solutions were shaken mechanically with 1% potassium hydroxide solution containing 10% of mannitol (cf. Criegee, Marchand, and Wannowius, *loc. cit.*). The colour of the methylene chloride solution faded and the aqueous solution became pink with potassium osmate. In some cases (pyrene, 3 : 4-benzpyrene, 1 : 2 : 5 : 6-dibenzanthracene) the methylene chloride solution remained somewhat coloured on account of quinone formation. Most of the diols were very sparingly soluble and partly came out of solution. The solid was filtered off and the remainder of the diol was recovered by evaporation of the methylene chloride solution. The diols, obtained in good yield, were recrystallised from benzene, chloroform, or methanol. It was found desirable to effect purification of some by chromatographic adsorption on alumina from benzene solution, followed by elution with chloroform. Most of the diols had poor power of crystallisation, and some of them tended to separate as gels from solutions in benzene or toluene. The diacetates, formed by brief boiling with acetic anhydride containing a little pyridine, were however well-crystallised colourless compounds. All the diols gave intense colours with concentrated sulphuric acid. The colours ranged from yellow or orange (pyrene, 3 : 4-benzpyrene) through scarlet or red (1 : 2-benzanthracene, 9 : 10-dimethyl-1 : 2-benzanthracene, 1 : 2 : 5 : 6-dibenzanthracene) to crimson (1'-methyl-, 5 : 9 : 10-trimethyl-1 : 2-benzanthracene) and intense purple (5 : 6 : 9 : 10-tetramethyl-1 : 2-benzanthracene). This last colour was especially persistent and lasted for several days. The diols from chrysene and 20-methylcholanthrene gave brown solutions in sulphuric acid.

3 : 4-*Dihydroxy*-3 : 4-*dihydro*-1 : 2-*benzanthracene* (X) formed colourless microscopic needles, m. p. 202—204° (decomp.) (Found: C, 82·6; H, 5·3. $C_{18}H_{14}O_2$ requires C, 82·45; H, 5·3%); its *diacetate* formed prisms, m. p. 142—143·5° (Found: C, 76·0; H, 5·1. $C_{22}H_{18}O_4$ requires C, 76·3; H, 5·2%). *Dihydroxy*-1'-*methyldihydro*-1 : 2-*benzanthracene* formed colourless silky needles (from benzene), m. p. 176—177° (Found: C, 82·8; H, 5·7. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%); its *diacetate* formed colourless rhombs, m. p. 145—146° (Found: C, 76·6; H, 5·6. $C_{23}H_{20}O_4$ requires C, 76·65; H, 5·6%). *Dihydroxy*-9 : 10-*dimethyldihydro*-1 : 2-*benzanthracene* formed long colourless needles (from methanol), m. p. 171—172° (Found: C, 82·95; H, 6·2. $C_{20}H_{18}O_2$ requires C, 82·75; H, 6·2%); its *diacetate* formed rhombs (from light petroleum), m. p. 153—153·5° (Found: C, 77·2; H, 5·7. $C_{24}H_{22}O_4$ requires C, 77·0; H, 5·9%). *Dihydroxy*-5 : 9 : 10-*trimethyldihydro*-1 : 2-*benzanthracene* formed colourless needles, m. p. 179—180° (Found: C, 82·6; H, 6·5. $C_{21}H_{20}O_2$ requires C, 82·9; H, 6·6%); a by-product, m. p. 187°, was formed in amount insufficient for complete purification. The *diacetate* from the pure diol formed thick rhombs (from light petroleum), m. p. 161—162° (Found: C, 77·5; H, 6·1. $C_{25}H_{24}O_4$ requires C, 77·3; H, 6·2%). The crude diol gave also by acetylation a compound which formed colourless leaflets, m. p. 209—210° (Found: C, 79·7; H, 6·0%). *Dihydroxy*-5 : 6 : 9 : 10-*tetramethyldihydro*-1 : 2-*benzanthracene* formed colourless needles (from light petroleum), m. p. 179—180° (Found: C, 83·3; H, 6·95. $C_{22}H_{22}O_2$ requires C, 83·0; H, 6·9%); its *diacetate* formed fine needles (from light petroleum), m. p. 156—157° (Found: C, 77·7; H, 6·3. $C_{26}H_{26}O_4$ requires C, 77·6; H, 6·5%). In this case the diol was obtained from the mother liquors of the crystallisation of the crude material from benzene. The compound which crystallised first from the benzene solution was a minor product which formed long colourless needles, m. p. 195—196° (Found: C, 78·5; H, 6·9%). *Dihydroxydihydro*-1 : 2 : 5 : 6-*dibenzanthracene* formed fine colourless needles (from toluene), m. p. *ca.* 200° (decomp.) (Found: C, 84·4; H, 5·0. $C_{22}H_{16}O_2$ requires C, 84·6; H, 5·1%); its *diacetate* was purified by chromatography on silica and formed colourless rhombs (from ethyl acetate), m. p. 176·5—177·5° (Found: C, 78·8; H, 5·1.

$C_{26}H_{20}O_4$ requires C, 78·75; H, 5·05%). *Dihydroxy-20-methyldihydrocholanthrene* formed a colourless solid (from benzene), m. p. *ca.* 215° (decomp.) (Found: C, 83·6; H, 5·8. $C_{21}H_{18}O_2$ requires C, 83·4; H, 6·0%); its *diacetate* formed needles, m. p. 210—211° (Found: C, 77·8; H, 5·8. $C_{25}H_{22}O_4$ requires C, 77·7; H, 5·7%). 1 : 2-*Dihydroxy*-1 : 2-*dihydrochrysene* (VIII), obtained by hydrolysis of the pure diacetate, formed an amorphous white solid (from benzene), m. p. *ca.* 180° (decomp.) (Found: C, 82·3; H, 5·4. $C_{18}H_{14}O_2$ requires C, 82·45; H, 5·3%); the *diacetate*, purified by chromatography on silica, formed needles (from light petroleum), m. p. 164—165° (Found: C, 76·5; H, 5·0. $C_{22}H_{18}O_4$ requires C, 76·3; H, 5·2%). 1 : 2-*Dihydroxy*-1 : 2-*dihydropyrene* formed an amorphous white solid (from benzene–light petroleum), m. p. *ca.* 178° (decomp.) (Found: C, 81·25; H, 5·25. $C_{16}H_{12}O_2$ requires C, 81·4; H, 5·1%) and gave a *diacetate* (purified by chromatography on silica and recrystallisation from light petroleum) as prisms, m. p. 146—147° (Found: C, 75·1; H, 4·9. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0%). The *diol* from 3 : 4-benzpyrene was very sensitive to atmospheric oxidation and all attempts at purification gave a pink amorphous product, m. p. 200—215° (decomp.) (Found: C, 83·5; H, 4·7. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·9%); its *diacetate* formed colourless prisms (from benzene), m. p. 214—215° (Found: C, 78·0; H, 4·9. $C_{24}H_{18}O_4$ requires C, 77·8; H, 4·9%).

Dehydration of the Diols and Formation of Methoxy-derivatives of the Hydrocarbons.—Dehydration was readily effected by dilute mineral acid. For example, a solution of the diol (0·1 g.) in acetic acid (3 c.c.) containing a few drops of concentrated hydrochloric acid was boiled for a few minutes, cooled, and diluted with water to precipitate the phenol. Most of the phenols were sensitive to atmospheric oxidation, so that the recrystallised products were contaminated with quinones. They were therefore characterised as their methyl ethers, prepared by methylation of the crude phenols with methyl sulphate in alkaline solution. These methyl ethers were usually purified by chromatography on alumina, followed by recrystallisation from light petroleum.

3-Methoxy-1 : 2-benzanthracene (cf. XI) formed colourless needles, m. p. 166—167°, not depressed by admixture with an authentic sample synthesised by the method of Fieser *et al.* (*loc. cit.*). Acetylation of the crude dehydration product of (X) gave 3-acetoxy-1 : 2-benzanthracene, m. p. 126—127° (Fieser and Dietz, *loc. cit.*, give m. p. 129°). In the chromatographic purification of this acetate there was isolated the 1 : 2-benz-3 : 4-anthraquinone of Fieser and Dietz, which was also obtained by chromic acid oxidation of the diol (X) in acetic acid.

3(?)-*Methoxy*-1′-*methyl*-1 : 2-*benzanthracene* formed colourless needles, m. p. 132—133° (Found: C, 88·2; H, 5·6. $C_{20}H_{16}O$ requires C, 88·2; H, 5·9%); 3(?)-*benzoxy*-1′-*methyl*-1 : 2-*benzanthracene* formed almost colourless fine needles, m. p. 192—193° (Found: C, 85·8; H, 5·05. $C_{26}H_{18}O_2$ requires C, 86·2; H, 5·0%). 3(?)-*Methoxy*-9 : 10-*dimethyl*-1 : 2-*benzanthracene* formed almost colourless rhombic plates, m. p. 129—130° (Found: C, 88·2; H, 6·2. $C_{21}H_{18}O$ requires C, 88·1; H, 6·3%); 3(?)-*methoxy*-5 : 9 : 10-*trimethyl*-1 : 2-*benzanthracene* formed pale yellow lances, m. p. 145—146° (Found: C, 87·8; H, 6·6; OMe, 10·0. $C_{22}H_{20}O$ requires C, 88·0; H, 6·7; OMe, 10·3%); 3(?)-*methoxy*-5 : 6 : 9 : 10-*tetramethyl*-1 : 2-*benzanthracene* formed long yellow needles, m. p. 164·5—165° (Found: C, 87·6; H, 6·9; OMe, 10·65. $C_{23}H_{22}O$ requires C, 87·9; H, 7·0; OMe, 10·4%). 3(?)-*Methoxy*-1 : 2 : 5 : 6-*dibenzanthracene* was purified through its crimson picrate, m. p. 183° (decomp.), and then formed fine colourless needles, m. p. 200—201° (Found: C, 89·5; H, 5·0. $C_{23}H_{16}O$ requires C, 89·6; H, 5·2%). 6(?)-*Methoxy*-20-*methylcholanthrene* (cf. XII) formed pale yellow needles, m. p. 204—205° (Found: C, 88·5; H, 6·3. $C_{22}H_{18}O$ requires C, 88·6; H, 6·0%). 2-Methoxychrysene (from IX) had m. p. 125—126°, not depressed by a specimen prepared through the 2-sulphonic acid (Newman and Cathcart, *J. Org. Chem.*, 1940, **5**, 621). 1-*Methoxypyrene* formed thick colourless prisms, m. p. 128—129° (Found: C, 87·8; H, 5·1; OMe, 13·9. $C_{17}H_{12}O$ requires C, 87·9; H, 5·2; OMe, 13·4%). This m. p. differed from those of the known 3- and 4-methoxypyrenes. For confirmation that the new compound, obtained through the diol, was the hitherto unknown 1-methoxypyrene, a specimen of this was prepared by a method which established its structure. For this purpose, *s*-hexahydropyrene (Cook and Hewett, *J.*, 1933, 398) was sulphonated with concentrated sulphuric acid at 70° (compare Schroeter, *Ber.*, 1924, **57**, 2022). The sodium sulphonate was fused with potash at 280—290°, the crude phenol was methylated with methyl sulphate and alkali, and the liquid product was dehydrogenated by heating with palladium-black at 270°. Chromatographic purification followed by recrystallisation then gave 1-methoxypyrene, m. p. 128—129° alone or mixed with the compound prepared from the diol formed by osmium tetroxide oxidation of pyrene.

Treatment of the diol from 3 : 4-benzpyrene gave a mixture of methoxybenzpyrenes. This was the only case in which there was any evidence of formation of more than one methoxy-compound by dehydration of a diol followed by methylation. The dihydroxydihydrobenzpyrene obtained by hydrolysis of its pure diacetate gave the same mixture of methoxybenzpyrenes as was formed from the crude diol. Partial separation of the mixture was effected by chromatography on alumina using light petroleum as solvent (coloured zones which appeared to contain quinones were also formed). The separated methoxybenzpyrenes were then converted into picrates, which were fractionally crystallised from benzene. In this way were obtained (*a*) brown needles, m. p. 173—174°, which were freed from picric acid to give a *methoxy*-3 : 4-*benzpyrene*, flat yellow needles (from light petroleum), m. p. 136—137° (Found: C, 89·5; H, 5·1. $C_{21}H_{14}O$ requires C, 89·4; H, 5·0; OMe, 11·0%); (*b*) brown needles, m. p. 178—179°, which yielded an isomeric *methoxy*-3 : 4-*benzpyrene* as small yellow needles (from light petroleum), m. p. 179·5—180° (Found: C, 89·3; H, 4·95; OMe, 11·4%). This isomeride was more strongly adsorbed on alumina than the compound, m. p. 136°, and its m. p. was strongly depressed by admixture with 4′-methoxy-3 : 4-benzpyrene, m. p. 183—184° (Fieser, Hershberg, and Newman, *J. Amer. Chem. Soc.*, 1935, **57**, 1509).

These experiments have been carried out by one of us (R. S.) working on behalf of the Oxford University Research Centre of the British Empire Cancer Campaign, to which we express our indebtedness. Microanalyses were made by Mr. J. M. L. Cameron.

UNIVERSITY OF GLASGOW. [*Received, March 14th*, 1947.]

43. *The Chemistry of the "Insoluble Red" Woods. Part II. A New Synthesis of 4-Hydroxycoumarins.*

By JOHN BOYD and ALEXANDER ROBERTSON.

A convenient method for the synthesis of 4-hydroxycoumarins by the condensation of *o*-hydroxyacetophenones with ethyl carbonate by means of sodium is described. The procedure is illustrated by its application to the preparation of various types of 4-hydroxycoumarin.

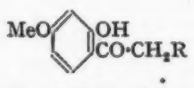
IN the course of experiments on the degradation of homopterocarpin (*J.*, 1940, 787), a product, $C_{15}H_9O_3(OMe)_3$, was obtained which it was considered might possibly be the 4-hydroxycoumarin (II), and during further work on the pterocarpin series and related topics it appeared highly desirable that the structure of this compound should be confirmed by synthesis. For this, a convenient method for the preparation of 4-hydroxycoumarins capable of being applied to the synthesis of 3-phenyl derivatives was required, and an examination of the literature showed that three main synthetical procedures have been described:

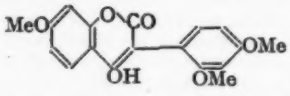
(A) The interaction of *o*-acetoxybenzoyl chlorides with ethyl sodio-malonate and -acetoacetate, yielding products capable of being degraded to the parent 4-hydroxycoumarins (Anschütz, *Ber.*, 1903, **36**, 465; *Annalen*, 1909, **367**, 169 and 289; cf. Heilbron and Hill, *J.*, 1927, 1705).

(B) The condensation of ethyl cyanoacetate with phenols according to the method of Hoesch (Sonn, *Ber.*, 1917, **50**, 1292; Bauer and Schroeder, *Arch. Pharm.*, 1921, **259**, 53).

(C) The cyclisation of suitable *o*-acyloxy-derivatives of benzoic esters with sodium at 160—165° (Pauly and Lockemann, *Ber.*, 1915, **48**, 28).

Of these methods (A) and (B) require the preparation of phenyl-substituted malonic esters for the synthesis of 4-hydroxy-3-phenylcoumarins, and (B) is also limited to the use of *m*-dihydric phenols and their derivatives. Moreover, the hydrolysis of the cyclic ketimines formed as intermediates in (B) is sometimes difficult to effect. On the other hand method (C) involves condensations with sodium at high temperatures and the yields are often erratic. The last procedure, which has been re-investigated by Jensen and Jensen (*Z. physiol. Chem.*, 1942, **277**, 66), who were unable to obtain the yields given by Pauly and Lockemann (*loc. cit.*), has been exhaustively explored by Stahmann, Wolff, and Link (*J. Amer. Chem. Soc.*, 1943, **65**, 2285) who state the optimum temperature for the condensation to be 240—250°.

(I.) 

 (II.)

In the present work it has been shown that *o*-hydroxyacetophenones and their ω-substituted derivatives (type I, when R = H, alkyl, or aryl), which are conveniently accessible, readily undergo condensation with absolute ethyl carbonate, or with ethyl carbonate containing 1—2% of alcohol, in the presence of sodium on the water-bath, affording a convenient general method for the synthesis of 4-hydroxycoumarins in good yield. The scope of the reaction is illustrated by its application to a variety of ketones, and as an example of the preparation of the parent hydroxycoumarins of this type from their methyl ethers it has been shown that *4-hydroxy-7-methoxy-3-phenylcoumarin* can be conveniently demethylated by means of boiling hydriodic acid, yielding *4 : 7-dihydroxy-3-phenylcoumarin*. The *coumarin* (II) has been obtained from the appropriate ketone (type I) by the general method, but it could not be equated with the isomeric oxidation product, $C_{15}H_9O_3(OMe)_3$, from homopterocarpin (*loc. cit.*).

EXPERIMENTAL.

4-Hydroxy-5 : 7-dimethoxycoumarin.—In the following condensations absolute ethyl carbonate or good quality commercial ethyl carbonate containing 1—2% of alcohol was employed.

A mixture of 2-hydroxy-4 : 6-dimethoxyacetophenone (Canter, Curd, and Robertson, *J.*, 1931, 1249) (1·5 g.), ethyl carbonate (40 ml.), and pulverised sodium (2·5 g.) was warmed on the steam-bath and 10 minutes later, when the vigorous reaction had ceased, sufficient methyl alcohol was added to destroy the excess of sodium, followed by ether (100—150 ml.). Extraction of the sodium salt of the product with water (30—40 ml.) and acidification with hydrochloric acid gave the *coumarin* which formed colourless needles (1·4 g.), m. p. 183°, from alcohol (Found: C, 59·3; H, 4·7. $C_{11}H_{10}O_5$ requires C, 59·5; H, 4·5%). Acetylation of the substance (0·2 g.) with acetic anhydride (2 ml.) and pyridine (1 ml.) at room temperature for 4 hours furnished the *acetate* which separated from dilute alcohol in elongated prisms, m. p. 175° (Found in material dried in a high vacuum at 80°: C, 59·3; H, 4·3. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·6%).

4-Hydroxy-7-methoxy-3-methyl- and *4-hydroxy-5 : 7-dimethoxy-3-methyl-coumarin* were prepared in the same way from 2-hydroxy-4-methoxy- (1·5 g.) and 2-hydroxy-4 : 6-dimethoxy-propiophenone (*J.*, 1931, 1251) (1·5 g.) respectively. The former compound crystallised from alcohol and then methyl alcohol in small needles (1·5 g.), m. p. 227° (Found : C, 64·3; H, 4·8. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%), and gave an *acetate*, forming prismatic needles, m. p. 131°, from aqueous alcohol (Found : C, 62·8; H, 5·0. $C_{13}H_{12}O_5$ requires C, 62·9; H, 4·8%). The latter compound separated from dilute alcohol in a mass of slender needles (1·4 g.), m. p. 176° (Found : C, 60·9; H, 5·2. $C_{12}H_{12}O_5$ requires C, 61·0; H, 5·1%), and yielded an *acetate* in elongated rods, m. p. 166°, from dilute alcohol (Found : C, 60·2; H, 4·9. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·0%).

When the appropriate ketones were employed the same general method gave almost theoretical yields of 4-hydroxycoumarin, m. p. 206° (Anschütz, *Annalen*, 1909, **367**, 162), 4-hydroxy-7-methylcoumarin, m. p. 217° (*ibid.*, p. 219), and 4-hydroxy-7-methoxycoumarin, m. p. 256° (Sonn, *loc. cit.*).

(With W. B. Whalley.) *4-Hydroxy-7 : 2′ : 4′-trimethoxy-3-phenylcoumarin* (II).—On being saturated with hydrogen chloride at 0° and then kept at room temperature for 3 days, a solution of 2 : 4-dimethoxybenzyl cyanide (Mitter and Maitra, *J. Indian Chem. Soc.*, 1936, **13**, 236) (2 g.) and resorcinol (3 g.) in ether (50 ml.) containing zinc chloride (2 g.) gave a crystalline ketimine hydrochloride which after being washed with ether and hydrolysed with water (60 ml.) on the steam-bath for 40 minutes yielded 2 : 4-dihydroxyphenyl 2 : 4-dimethoxybenzyl ketone, m. p. 152° after purification; yield of pure material, 1·2 g., the m. p. of which was unchanged after repeated crystallisation (cf. Späth and Schläger, *Ber.*, 1940, **73**, 1, who obtained a poor yield of material, the m. p. of which was stated to be 156°). Methylation of this ketone (2·5 g.) with methyl iodide (0·8 ml.) and potassium carbonate (3 g.) in boiling acetone (50 ml.) during 70 minutes gave *ω*-2 : 4-dimethoxyphenyl-4-*O*-methylresacetophenone (2·5 g.), m. p. 116° (Found : C, 67·8; H, 6·1. Calc. for $C_{17}H_{18}O_5$: C, 67·5; H, 6·0%), (cf. Späth and Schläger, *loc. cit.*, who give m. p. 114—115°).

Interaction of the foregoing methyl ether (0·5 g.) with ethyl carbonate (50 ml.) and pulverised sodium (0·5 g.) at room temperature and then on the steam-bath for ½ hour gave, on isolation with aid of ether and water, the *coumarin* (II) which formed colourless prisms (0·45 g.), m. p. 200°, from alcohol having a negative ferric reaction (Found : C, 65·8; H, 4·8. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%). Methylation of this compound (0·5 g.) with methyl iodide (0·3 g.), and potassium carbonate (1 g.) in boiling acetone (60 ml.) during one hour furnished a quantitative yield of *4 : 7 : 2′ : 4′-tetramethoxy-3-phenylcoumarin* which crystallised from aqueous alcohol in needles, m. p. 152° [Found : C, 66·5; H, 5·4; OMe, 36·8. $C_{18}H_6O_2(OMe)_4$ requires C, 66·7; H, 5·3; OMe, 36·2%]. The *O-acetyl* derivative of (II) formed thick rhombic plates, m. p. 157°, from dilute alcohol (Found : C, 65·1; H, 4·9. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

4 : 7-Dihydroxy-3-phenylcoumarin.—Interaction of (I, R = Ph) (3 g.) with ethyl carbonate (50 ml.) and sodium (2 g.) at room temperature during 14 hours gave rise to *4-hydroxy-7-methoxy-3-phenylcoumarin* which separated from benzene in clusters of plates (2 g.), m. p. 204° (Found : C, 71·4; H, 4·6. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%), and on methylation gave *4 : 7-dimethoxy-3-phenylcoumarin*, forming needles, m. p. 105°, from methyl alcohol [Found : C, 72·1; H, 4·9; OMe, 21·4. $C_{15}H_8O_2(OMe)_2$ requires C, 72·3; H, 5·0; OMe, 21·9%]. The *acetate* of the hydroxycoumarin crystallised from methyl alcohol in platelets, m. p. 160° (Found : C, 69·5; H, 4·5. $C_{18}H_{14}O_5$ requires C, 69·7; H, 4·5%). Similarly, 2-hydroxy-4-benzyloxyphenyl benzyl ketone (Venkataraman *et al.*, *J.*, 1934, 1121) (1·5 g.) gave *4-hydroxy-7-benzyloxy-3-phenylcoumarin*, forming clusters of prismatic needles (1·5 g.), m. p. 259—260° (decomp.), from alcohol (Found : C, 76·4; H, 4·8. $C_{22}H_{16}O_4$ requires C, 76·7; H, 4·7%). This substance, which is sparingly soluble in acetic acid, gave an *acetate*, crystallising in plates, m. p. 153, from dilute alcohol (Found : C, 74·6; H, 4·6. $C_{24}H_{18}O_5$ requires C, 74·4; H, 4·7%).

Demethylation of 4-hydroxy-7-methoxy-3-phenylcoumarin (0·5 g.) with a gently boiling mixture of hydriodic acid (10 ml., *d* 1·7), acetic anhydride (5 ml.), and acetic acid (5 ml.) during 20—25 minutes, and subsequent addition of water (70 ml.) to the cold solution, yielded *4 : 7-dihydroxy-3-phenylcoumarin* which separated from methyl alcohol–chloroform and then methyl alcohol in clusters of elongated prisms, m. p. 284—285° (decomp.), having a negative ferric reaction (Found : C, 70·8; H, 4·2. $C_{15}H_{10}O_4$ requires C, 70·9; H, 3·9%).

The following new 4-hydroxycoumarins and their derivatives have also been prepared by the general method from the requisite ketones in almost theoretical yield :

4-Hydroxy-7 : 4′-dimethoxy-3-phenylcoumarin, prismatic needles, m. p. 219—220°, from alcohol (Found : C, 68·2; H, 4·7. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%), yielding a 4-O-*methyl ether*, irregular plates, m. p. 165°, from alcohol [Found : C, 69·2; H, 5·3; OMe, 28·8. $C_{15}H_7O_2(OMe)_3$ requires C, 69·2; H, 5·1; OMe, 29·8%], and an *acetate*, needles, m. p. 164°, from alcohol (Found : C, 67·1; H, 4·9. $C_{19}H_{16}O_6$ requires C, 67·0; H, 4·7%).

4-Hydroxy-7 : 3′ : 4′-trimethoxy-3-phenylcoumarin, tiny needles, m. p. 212°, from alcohol (Found : C, 65·7; H, 5·0. $C_{18}H_{16}O_6$ requires C, 65·9; H, 4·9%), forming an O-*methyl ether*, needles, m. p. 163°. from alcohol [Found : C, 66·3; H, 5·4; OMe, 35·5. $C_{15}H_4O_4(OMe)_4$ requires C, 66·7; H, 5·3; OMe, 36·2%], and an *acetate*, platelets, m. p. 194°, from aqueous alcohol (Found : C, 64·7; H, 5·0. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

4-Hydroxy-7-methoxy-3-(3′ : 4′-methylenedioxyphenyl)coumarin, needles, m. p. 256°, from methyl alcohol (Found : C, 65·6; H, 3·9. $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·8%), yielding an O-*methyl* derivative, needles, m. p. 186—187°, from alcohol [Found : C, 66·0; H, 4·5; OMe, 17·8. $C_{16}H_8O_4(OMe)_2$ requires C, 66·3; H, 4·3; OMe, 19·0%], and an *acetate*, tiny needles, m. p. 157°, from alcohol (Found : C, 64·2; H, 4·1. $C_{19}H_{14}O_7$ requires C, 64·4; H, 4·0%).

2-Hydroxy-4-methoxyphenyl 3 : 4-dimethoxybenzyl ketone required for the synthesis of the corresponding coumarin was prepared as follows. Condensation of homoveratronitrile (4 g.) with resorcinol (6 g.) in ether (140 ml.) by means of zinc chloride (2 g.) and hydrogen chloride and hydrolysis of the resulting ketimine with water (100 ml.) on the steam-bath for 40 minutes gave *2 : 4-dihydroxyphenyl 3 : 4-dimethoxybenzyl ketone* which crystallised from alcohol in colourless plates (3·2 g.), m. p. 180°, having a cherry-red

ferric reaction in alcohol (Found: C, 66·9; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). Methylation of this compound (2 g.) with methyl iodide (0·6 g.) and potassium carbonate (2·5 g.) in boiling acetone (80 ml.) during 70 minutes gave the 4-*O*-methyl ether which separated from light petroleum (b. p. 60—80°) in colourless needles (1·8—1·9 g.), m. p. 118°, having a brown ferric reaction [Found: C, 67·2; H, 6·1; OMe, 30·5. $C_{14}H_9O_2(OMe)_3$ requires C, 67·5; H, 6·0; OMe, 3·07%].

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UNIVERSITY OF LIVERPOOL. [*Received, March 11th*, 1947.]

44. *Degradation of α-Amino-acids to Aldehydes and Ketones by Interaction with Carbonyl Compounds.*

By ALEXANDER SCHÖNBERG, RADWAN MOUBASHER, and AKILA MOSTAFA (MRS. SAID).

α-Amino-acids are degraded to the corresponding aldehydes or ketones containing one less carbon atom (*e.g.*, phenylaminoacetic acid ⟶ benzaldehyde) by the action of certain carbonyl compounds. Tables I and II respectively contain a list of the active and the inactive carbonyl compounds; they show that active agents must contain the grouping ·CO·[CH:CH]$_n$·CO·, where $n = 0$ or an integer, and that at least one carbonyl group must be aldehydic or ketonic. A proposed reaction mechanism is illustrated in the scheme on p. 178.

The antibacterial effect of 2-hydroxy-2′-methoxybenzil seems to be connected with its power of bringing about the above degradation.

Priority claims in respect of the synthesis of this substance are made.

SINCE Strecker's observation (*Annalen*, 1862, **123**, 363) that alloxan reacts with alanine to give carbon dioxide and acetaldehyde, a number of carbonyl compounds have been found which degrade α-amino-monocarboxylic acids, leaving the corresponding aldehyde or ketone with one less carbon atom, the latter being eliminated in the form of carbon dioxide. The reaction is carried out by treating the amino-acid with the carbonyl compound in aqueous solution or in suspension; only reactions of this type are described as Strecker degradations in this paper; the term does not refer to the degradation of α-amino-acids to aldehydes by the action of peroxides, catalysts, or enzymes.

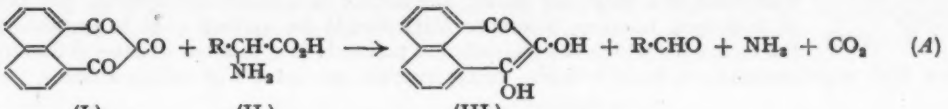
A detailed investigation of this degradation seemed justified because, *inter alia*, substances of much pharmacological interest are capable of effecting it, *e.g.*, dehydroascorbic acid, alloxan, and 2-methyl-1 : 4-naphthaquinone. Our results may be grouped as follows: (*a*) the relationship between the constitution of α-amino-acids and their power to undergo the Strecker degradation, (*b*) the final fate of the amino-group originally present in the α-amino-acids, (*c*) the relationship between the constitution of the carbonyl compounds and their power to effect this degradation, and its mechanism.

Nature of α-Amino-acids with which the Strecker Degradation may be carried out.—It has been established that the two hydrogen atoms attached to the nitrogen atom must be unsubstituted. We found that sarcosine (*N*-methylglycine) does not produce any aldehyde or ketone when boiled with "ninhydrin" (hydrate of V) or *peri*naphthindanetrione (I), which are strong agents in the Strecker degradation; further, proline, which is an *N*-substituted cyclic α-amino-acid, does not undergo the degradation when treated with ninhydrin (Grassmann and Arnim, *Annalen*, 1934, **509**, 288). On the other hand, the hydrogen atom attached to the α-carbon atom in (II) may be substituted; thus amino*iso*butyric acid yields acetone when treated with *p*-benzoquinone (Langenbeck, *Ber.*, 1928, **61**, 942), with methylglyoxal (Neuberg and Kobel, *Biochem. Z.*, 1927, **188**, 197), with ninhydrin, or with *peri*naphthindanetrione.

It seems that the Strecker degradation is a general reaction with all α-amino-acids having the structure (II), though glycine was not supposed to give formaldehyde when treated with ninhydrin (Ruhemann, *J.*, 1911, **99**, 1492; Abderhalden, *Z. physiol. Chem.*, 1938, **252**, 81). However, we obtained a good yield of formaldehyde when a glycine solution was allowed to react dropwise with a boiling ninhydrin solution in such a way that the formaldehyde formed was directly driven off with steam [see also p. 179, ref. (23)].

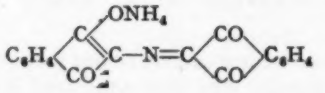
Final Fate of the Amino-group of the α-Amino-acid subjected to the Strecker Degradation.—This depends on the nature of the carbonyl compound employed: (*a*) The amino-group may be eliminated in the form of ammonia; this is, *e.g.*, the case when α-amino-acids are degraded by the action of *peri*naphthindanetrione (I), in which case dihydroxy*peri*naphthindenone (III) is precipitated and thus removed from the sphere of the reaction. (*b*) The amino-group may become linked to the carbonyl compound which effects the degradation, converting it into an

amino-compound of similar structure; thus, alanine is formed when α-aminophenylacetic acid is subjected to degradation by the action of pyruvic acid (Herbst and Engel, *J. Biol. Chem.*,



(I.) (II.) (III.) (*A*)

1934, 107, 505; Herbst, " The Transamination Reaction ", in " Advances in Enzymology ", Vol. 4, p. 77, New York, 1946). (*c*) The amino-group may enter into combination with the carbonyl compound used as the degrading agent, producing a nitrogenous compound of rather complicated character, not closely related to the original compound. Thus when triketoindane (V) is used in the Strecker degradation it becomes transformed into a violet-blue imino-compound (IV) * (Grassmann and Arnim, *loc. cit.*; compare also Gilman, " Organic Chemistry ", 2nd edtn., Vol. II, 1099, and Virtanen *et al.*, *Z. physiol. Chem.*, **1940, 266, 193**).



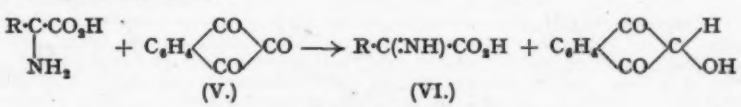
(IV.)

Nature of Carbonyl Compounds which bring about the Strecker Degradation.—Table I lists 36 substances which are active agents in this degradation, 21 being recorded by us for the first time. Table II gives the names of carbonyl compounds which cannot be used as agents in this reaction; for almost all of them this had not hitherto been reported.

Tables I and II reveal that the degradation cannot be effected by monocarbonyl compounds, but only by those containing the group ·CO·[CH:CH]$_n$·CO·; the double bond in which may be of an aromatic character. Nevertheless, not all substances containing this group effect the degradation; *e.g.*, parabanic acid (Traube, *loc. cit.*), *s*-dibenzoylethylene, and dibenzoylstilbene. The reason for this is that, when treated with primary amines in aqueous media, these and related substances do not form Schiff's compounds, the formation of which is the first and essential step in the degradation (see *B*). *cis*- and *trans*-*s*-Dibenzoylethylene, for example, react with primary amines by addition at the double bond; thus with aniline they form Ph·CO·CH$_2$·CH(NHPh)·COPh (Paal and Schulze, *Ber.*, 1900, **33**, 3799). So far all substances found to be active in the Strecker degradation are either aldehydic or ketonic.

Since the degradation can only be brought about by substances containing the group ·CO·[CH:CH]$_n$·CO·, this reaction can be used to ascertain the occurrence of such a grouping, but, as not all substances containing this grouping effect this degradation, this test is of diagnostic value only when positive.

Reaction Mechanism of the Strecker Degradation.—Obviously, all reaction schemes ignoring the above grouping have to be abandoned. Among those is that of Grassmann and Arnim (*loc. cit.*), which shows the α-imino-acid (VI) as an intermediate and triketoindane functioning only as a dehydrogenating agent:

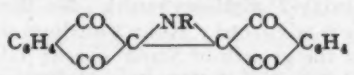


(V.) (VI.)

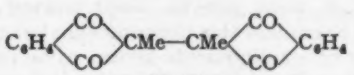
$$R\cdot C(:NH)\cdot CO_2H \xrightarrow{H_2O} R\cdot CHO + NH_3 + CO_2$$

Again if the degradation be due to direct dehydrogenation, it would be difficult to explain why it is brought about by such weak dehydrogenating agents as anthraquinone and not by the stronger dehydrogenating agents azobenzene and methylene-blue.

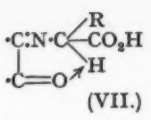
* For this compound the formulæ (IV*a*) and (IV*b*) have been advanced by Woker and Antener (*Helv. Chim. Acta*, 1937, **20**, 1260) without experimental proof. These formulæ are highly improbable, because substances of such structure should not be violet or blue [compare (IV*c*), which is colourless; Gabriel and Leupold, *Ber.*, 1898, **31**, 1159].



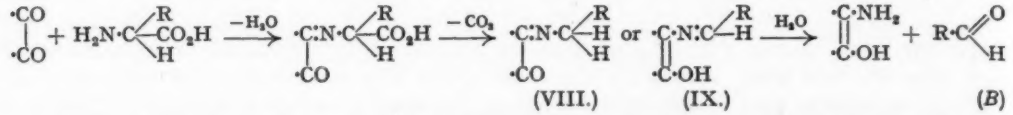
(IV*a*, R = H; IV*b*, R = NH$_4$.)



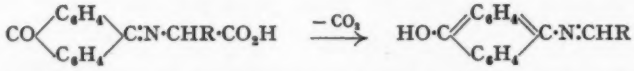
(IV*c*.)


(VII.)

The following scheme (*B*) is advanced for the mechanism: (VIII) and (IX) are isomers according to classical views, but they may be considered as extreme structures of a molecule having the nature of a resonance hybrid; the theory of hydrogen bonding (compare VII) should be applied. It is possible that the ease with which the degradation proceeds in a number of cases is due to the fact that the intermediate Schiff's bases, being hybrids, are ketonic as well as enolic.

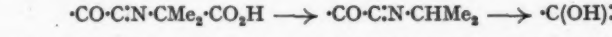

(VIII.) (IX.) (*B*)

A similar scheme may be proposed for the vinylogues, *i.e.*, 1 : 4-dicarbonyl compounds. In the case of anthraquinone, the essential part of the reaction involved in the degradation is as follows:

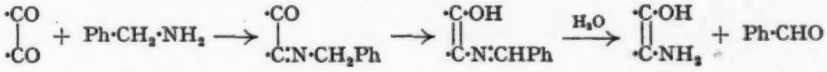


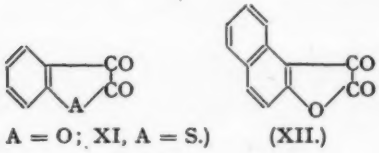
On the other hand, a similar mechanism cannot be put forward for the action of α-amino-acids on dibenzoylmethane, and this explains why this compound is incapable of bringing about the degradation.

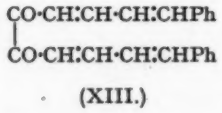
It is shown from scheme (*B*) that in accordance with the experimental results the two hydrogen atoms of the amino-group are essential for the Strecker degradation. The third hydrogen atom, attached to the α-carbon atom bearing the amino-group, which is also necessary, is either that already present in the amino-acid from the beginning, as in the case of alanine, or is formed during the reaction as the result of decarboxylation, as in the case of amino*iso*butyric acid. It is well known that α-imino-acids have a strong tendency to split off CO_2 (Wieland and Bergel, *Annalen*, 1929, **439**, 196):

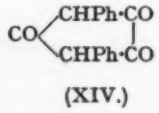

(*C*)

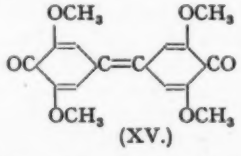
Scheme (*B*) connects the formation of aldehydes from α-amino-acids in the degradation with the formation of aldehydes from non-acidic substances, as in the formation of benzaldehyde from benzylamine by the action of alloxan or isatin (Traube, *loc. cit.*):

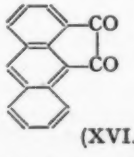


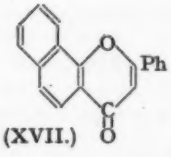

(X, A = O; XI, A = S.) (XII.)


(XIII.)


(XIV.)


(XV.)


(XVI.)


(XVII.)

2-Hydroxy-2′-methoxybenzil and the Strecker Degradation.—Kuhn, Birkofer, and Moller (*Ber.*, 1943, **76**, 900) describe the action of 2-hydroxy-2′-methoxybenzil on *Staphylococcus aureus*. (They overlook the fact that this benzil derivative had already been prepared by Schönberg and Kraemer, *Ber.*, 1922, **55**, 1185, by an almost identical method.) They found that cultures growing on a synthetic medium containing as nitrogenous supplement only organic nitrogenous compounds (apart from a small amount of arginine nitrate), amongst them being a number of α-amino-acids, such as *dl*-alanine, *dl*-leucine, and *dl*-phenylalanine, were greatly hindered in their growth when treated with 2-hydroxy-2′-methoxybenzil. No theory was proposed to explain this phenomenon, but the following is advanced: Kuhn's medium contained a number of α-amino-acids known to be important for the growth of *Staph. aureus* (Gladstone, *Brit. J. Exp. Path.*, 1937, **18**, 322), and we have found (see above) that, in experiments carried

TABLE I.

Carbonyl compounds which are active agents in the Strecker degradation. The amino-acids mentioned in the footnotes indicate that each of them has been transformed into the corresponding aldehyde or ketone containing one less carbon atom, and that they have been separated as such or as derivatives.

Section I, ·CO·CO· type.

Glyoxal [1, 17]
Methylglyoxal [2, 17]
Pyruvic acid [3]
Diacetyl [4, 17]
Alloxan [5]
(α-Ketoglutardialdehyde) [22]
(*o*-Benzoquinone and derivatives) [6]
Dehydroascorbic acid [7, 17]
Dimethylalloxan [8]
Coumarandione (X) [17]
Thiacoumarandione (XI) [17]
Isatin [9]
Phenylglyoxal [10, 16]
Phenylglyoxylic acid [16]
Triketoindane (V) [11, 19, 20, 23]
Phenylpyruvic acid [12]
Camphorquinone [17]
Acenaphthenequinone [17]
β-Naphthacoumarandione (XII) [17]
*peri*Naphthindanetrione (I) [17, 18, 20]
Phenanthraquinone [17]
Benzil [16]
Diphenyl triketone [16]
2-Hydroxy-2′-methoxybenzil [17]
Aceanthraquinone (XVI) [17]
Oxalyl dibenzyl ketone (XIV) [16]
Retenequinone [17]
4 : 4′-Bisdimethylaminobenzil [16]
Di-(ω-phenylbutadienyl) diketone (XIII) [15, 17]

Section II, ·CO·[CH:CH]·CO· type.

Benzoquinone [13]
Toluquinone [14]
2-Methyl-1 : 4-naphthaquinone [17]
Anthraquinone [17]
Thioindigo [17]
Indigo [17]

Section III, ·CO·[CH:CH]$_2$·CO· type.

Coerulignone (XV) [17]

[1] Neuberg and Kobel, *Biochem. Z.*, 1927, **185**, 477 (alanine).

[2] *Idem, ibid.*, **188**, 197 (alanine, amino*iso*butyric acid, leucine, phenylaminoacetic acid).

[3] Herbst and Engel, *loc. cit.* (glycine, phenylalanine, phenylaminoacetic acid); Herbst, *loc. cit.* (alanine, leucine, *p*-methoxyphenylalanine).

[4] Neuberg and Kobel, see (1). They stress the importance of their finding diacetyl as a metabolic product (*Biochem. Z.*, 1927, **188**, 198).

[5] Strecker, *loc. cit.* (alanine); Hurtley and Wootton, *J.*, 1911, **99**, 288 (glycine, alanine, leucine, α-aminobutyric acid); Traube, *loc. cit.* (phenylaminoacetic acid); Abderhalden, *loc. cit.* (valine, alanine, α-aminobutyric acid).

[6] Schaaf, *Biochem. Z.*, 1929, **205**, 449 (alanine in presence of catechol and oxygen yields acetaldehyde, *o*-benzoquinone is believed to be an intermediate). Berrenscheen and Danzer (*Z. physiol. Chem.*, 1933, **220**, 57) obtained formaldehyde when glycine was treated in presence of oxygen with *o*-$C_6H_4(OH)_2$, 3 : 4-$(OH)_2C_6H_3$·CO·CH_2·NH_2, 3 : 4-$(OH)_2C_6H_3$·CO·CH_2·NHMe, and 3 : 4-$(OH)_2C_6H_3$·CO·CH_2·NHEt. Formaldehyde was also produced with adrenaline in a similar experiment (Edlbacher and Kraus, *ibid.*, 1928, **178**, 239).

[7] Abderhalden, *Fermentforschung*, 1937, **15**, 360; he allowed ascorbic acid, in the presence of oxygen, to react with glycine and alanine and obtained the corresponding aldehyde with one less carbon atom. He discussed (p. 361) whether the Strecker degradation was brought about by ascorbic acid itself or by dehydroascorbic acid, but left the question open. *Idem, ibid.*, 1938, **15**, 522 (α-aminobutyric acid, norvaline, valine, norleucine, leucine, *iso*leucine, phenylalanine).

[8] Hurtley and Wootton, *loc. cit.* (names of amino-acids not given).

[9] Traube, *loc. cit.* (phenylaminoacetic acid); Abderhalden, *Z. physiol. Chem.*, 1938, **252**, 81 (alanine, α-aminobutyric acid, norvaline, valine, leucine, *iso*leucine, norleucine, phenylalanine).

[10] Neuberg and Kobel, *loc. cit.* (alanine). The formation of formaldehyde by the action of glycine on phenylglyoxal was proved by colour reaction and by titration (*Biochem. Z.*, 1927, **188**, 197).

[11] Ruhemann, *loc. cit.* (alanine); Virtanen *et al.*, *loc. cit.* (alanine, valine, leucine, *iso*leucine, phenylalanine, methionine); compare Abderhalden, *loc. cit.* (leucine, alanine, α-aminobutyric acid).

[12] Herbst and Engel, *loc. cit.* (phenylaminoacetic acid).

[13] Traube, *loc. cit.* (phenylaminoacetic acid; he failed to obtain benzaldehyde when he worked with chloranil); Wieland and Bérgel, *loc. cit.* (alanine); Langenbeck, *loc. cit.* (amino*iso*butyric acid).

[14] Traube, *loc. cit.* (phenylaminoacetic acid).

[15] Karrer and Cochand, *Helv. Chim. Acta*, 1945, **28**, 1181 (method of preparation).

[16] This paper (alanine).

[17] This paper (phenylaminoacetic acid).

[18] This paper (valine, leucine, phenylalanine, amino*iso*butyric acid).

[19] This paper (amino*iso*butyric acid).

[20] This paper (glycine).

[21] Traube, *loc. cit.* (phenylaminoacetic acid).

[22] Akabori (*Ber.*, 1933, **66**, 143) believes that α-ketoglutardialdehyde is formed when a pentose or furfuraldehyde is allowed to react with an α-amino-acid; a corresponding substance is believed to be produced when glucose is used in place of a pentose. Akabori is of the opinion that the action of α-ketoglutardialdehyde and related substances may be explained by the formation of a peroxide form , which has an oxidising action on the α-amino-acids.

[23] MacFadyen (*J. Biol. Chem.*, 1945, **158**, 132) has shown that ninhydrin at pH 1 evolves 0·81 mol. of formaldehyde from glycine, measurable by the chromotropic acid procedure.

TABLE II.

Carbonyl compounds which are not active in the Strecher degradation. (The footnotes indicate the the amino-acids which were tried without success.)

Urea [17]	Benzophenone [16]
Oxamide [17]	Benzoin [16]
Parabanic acid [17, 21]	Benzylideneacetophenone [16]
Piperonal [17]	Dibenzoylmethane [16]
Coumarin [17]	Dibenzoylethylene [16]
Phorone [17]	Dibenzylideneacetone [16]
Camphor [16]	α-Naphthaflavone (XVII) [16]
Fluorenone [16]	Dibenzoylstilbene [16]
Xanthone [17]	

out under physiological conditions of temperature and pH, 2-hydroxy-2′-methoxybenzil converts α-amino-acids into the corresponding aldehydes containing one less carbon atom; it is believed that the same reactions took place also in the synthetic medium used by Kuhn, and that growth was hindered because the essential α-amino-acids were destroyed by the action of 2-hydroxy-2′-methoxybenzil.

It is also possible that 2-hydroxy-2′-methoxybenzil shows "Strecker activity" towards essential enzyme systems (connected with *Staph. aureus*) which are thus degraded.

Kuhn *et al.* found that the growth of *Staph. aureus* was not hindered indefinitely by addition of 2-hydroxy-2′-methoxybenzil to the culture, for when it was used in a concentration of $3{\cdot}0 \times 10^{-5}$ and $5{\cdot}0 \times 10^{-5}$ g., per c.c. of culture, growth was completely inhibited only for 48 and for 96 hours respectively. This can be explained on the basis of the above theory that the inhibition of growth is due to elimination from the medium of α-amino-acids important for growth if Gladstone's results are taken into consideration. He found that *Staph. aureus* grew on a medium containing glycine, valine, leucine, proline, phenylalanine, tyrosine, methionine, aspartic acid, lysine, arginine, histidine, and cystine, but that no growth occurred for 24 hours or even longer if the phenylalanine was omitted. After 96 hours, however, good growth, in some cases maximum growth, was observed. Similar results were obtained when a medium was used containing the above mentioned amino-acids, including phenylalanine, but without glycine or valine or leucine.

The mechanism of the action of the antibiotic effect of some *p*-quinones is now under discussion (Hoffman-Ostenhof and Blach, *Experientia*, 1946, **2**, 405; Hoffman-Ostenhof, *Science*, 1947, **105**, 549; cf. also Oxford, *J. Soc. Chem. Ind.*, 1942, **61**, 48, 189). The hypothesis is advanced that the action may be explained as above in the case of 2-hydroxy-2′-methoxybenzil. The antibiotic action of certain quinones has hitherto been connected with their activity in interfering with sulphhydryl groups of enzymes concerned in bacterial metabolism; another possible mechanism has been derived from the relatively high oxidation–reduction potential of these quinones, which are believed to act as antibiotics by interfering with bacterial respiratory enzymes.

EXPERIMENTAL.

The Strecker degradation was principally carried out by allowing the amino-acid to react with the carbonyl compound dissolved or suspended in boiling water for 15 minutes in an atmosphere of carbon dioxide. The detailed procedure varied according to the nature of the carbonyl compound used, *e.g.*, its solubility and volatility and also the nature of the amino-acid; the main variations were as follows: (*a*) When the carbonyl reagent was soluble in water and not volatile in steam, the procedure was similar to that described in the case of *peri*naphthindanetrione and phenylaminoacetic acid. (*b*) When the degrading reagent was volatile in steam, an excess of the amino-acid was refluxed with the carbonyl compound for 15 minutes; on distillation of the reaction mixture, the aldehyde or ketone formed, and not the degrading reagent, passed over with steam. (*c*) When the carbonyl compound was sparingly soluble in water, the procedure was usually similar to that described in the case of anthraquinone and phenylaminoacetic acid or of diphenyl triketone and alanine. The addition of glycerol served to facilitate the wetting of the carbonyl compound, or to increase its solubility. Glycerol was chosen because it is soluble in water, has no chemical action on the α-amino-acids or the carbonyl compounds used, and is not steam-volatile. The degradation reactions are grouped below according to the method used.

The aldehyde or ketone formed was converted into its phenyl- or 2 : 4-dintrophenyl-hydrazone, and identified by m. p. and mixed m. p. Benzaldehyde was also identified by the red colour of the phenylhydrazone when exposed to the sun.

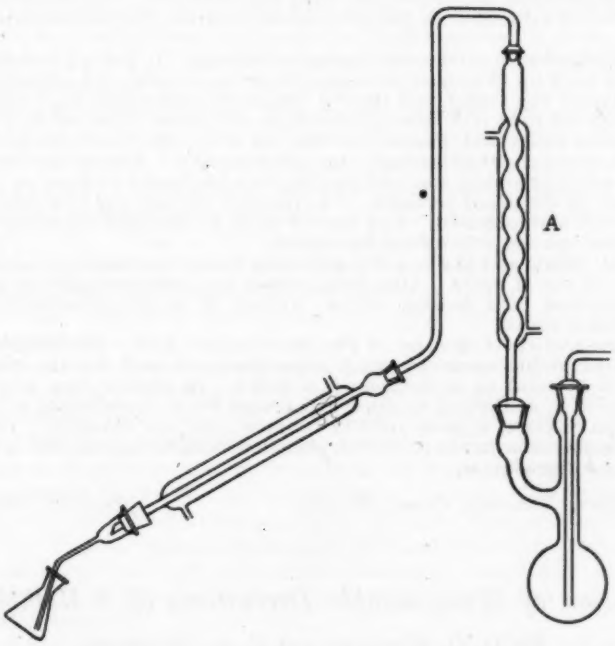
In all experiments, provided that the degradation took place at all, the yield was over 25% of the theoretical; no conclusion can be drawn from the yield as to the velocity of the various degradations owing to the differences in the conditions of reaction.

Action of Phenylaminoacetic acid on Dehydroascorbic Acid, Acenaphthenequinone, peri*Naphthindanetrione* (I), *and Aceanthraquinone* (XVI).—*peri*Naphthindanetrione (0·78 g.) (Errera, *Gazzetta*, 1913, **43**, I, 584; **44**, II, 18), phenylaminoacetic acid (1 g.), and water (100 c.c.) were boiled for 15 mins. in a stream

of carbon dioxide in a distilling flask provided with a condenser dipping into 50 c.c. of alcohol containing 0·5 g. of 2 : 4-dinitrophenylhydrazine. At the end of the experiment the contents of the receiver were warmed for some time, treated with 15 c.c. of concentrated hydrochloric acid, and left to cool. Benzaldehyde 2 : 4-dinitrophenylhydrazone was precipitated, crystallised from alcohol, and identified by m. p. and mixed m. p. (Found : C, 54·3; H, 3·7; N, 20·1. Calc. for $C_{13}H_{10}O_4N_4$: C, 54·5; H, 3·5; N, 19·6%).

The experiments with the other three compounds were carried out essentially as above, but the condenser dipped into ice-cold water to trap any benzaldehyde developed in the reaction, and the distillate was finally treated with an aqueous-alcoholic solution of phenylhydrazine hydrochloride; in all cases benzaldehyde phenylhydrazone was formed.

Action of peri*Naphthindanetrione* (I) *on Valine, Leucine, Phenylalanine, and Sarcosine.*—The trione was treated with these four amino-acids severally under the above conditions for its reaction with phenylaminoacetic acid. *iso*Butaldehyde, *iso*valeraldehyde, and phenylacetaldehyde were obtained from the first three amino-acids and identified as 2 : 4-dinitrophenylhydrazones (Found : C, 47·6; H, 4·8; N, 21·8. Calc. for *iso*butaldehyde dinitrophenylhydrazone, $C_{10}H_{12}O_4N_4$: C, 47·6; H, 4·8; N, 22·2%. Found : C, 49·8; H, 5·1; N, 20·9. Calc. for *iso*valeraldehyde dinitrophenylhydrazone, $C_{11}H_{14}O_4N_4$: C, 49·6; H, 5·3; N, 21·0%), but sarcosine did not give an aldehyde or ketone.



Action of Phenylaminoacetic Acid on Glyoxal, Methylglyoxal, Pyruvic Acid, and Diacetyl.—Phenylaminoacetic acid (1½—2 mols.) was treated with each of the four carbonyl compounds (1 mol.), and the mixture refluxed for 15 minutes using a very efficient refluxing condenser and then distilled. The distillate was treated with phenylhydrazine hydrochloride and in all cases benzaldehyde phenylhydrazone was precipitated.

Action of Phenylaminoacetic Acid on Coumarandione (X), *Thiocoumarandione* (XI), *Camphorquinone, β-Naphthacoumarandione* (XII), *Phenanthraquinone, Retenequinone, Di-(ω-phenylbutadienyl) Diketone* (XIII), *2-Methyl-1 : 4-naphthaquinone, Anthraquinone, Indigo, Thioindigo, and Coerulignone* (XV).—The amino-acid was refluxed with the carbonyl compound in aqueous glycerol (100 c.c. glycerol; 25—100 c.c. water) in a stream of carbon dioxide for 30 mins. An efficient condenser was used for refluxing, its upper end being connected with a tube dipping into an aqueous-alcoholic solution of phenylhydrazine hydrochloride to trap any benzaldehyde. When the reaction mixture was distilled, benzaldehyde was obtained in all cases.

Phenylaminoacetic Acid and Urea, Oxamide, Parabanic Acid, Piperonal, Coumarin, Phorone, Fluorenone, Xanthone, and Benzoin.—In similar experiments to those just described, except that glycerol was omitted in that with urea, benzaldehyde could not be detected.

Action of Alanine on Phenylglyoxal, Phenylglyoxylic Acid, Benzil, Diphenyl Trihetone, Oxalyl Dibenzyl Ketone (XIV) *and 4 : 4′-Bisdimethylaminobenzil.*—Alanine and the carbonyl compound were refluxed with 100 c.c. of *ca.* 50% aqueous glycerol in the apparatus shown in the figure. For the first 15 minutes water was passed through the condenser *A*, then *A* was emptied and heating was continued for another 10 minutes. The above procedure was followed to ensure that the acetaldehyde formed in the process would pass over with steam. It was detected in each case in the receiver by means of its 2 : 4-dinitrophenylhydrazone.

Alanine and Camphor, Benzophenone, Benzoin, Benzylideneacetophenone, Dibenzoylmethane, Dibenzoylethylene (m. p. 111°), *Dibenzylideneacetone, α-Naphthaflavone* (XVII), *and Dibenzoylstilbene.*—Under similar conditions to the last experiments, acetaldehyde could not be detected.

Action of α-Aminoisobutyric Acid on Ninhydrin and peri*Naphthindanetrione* (I).—The experiments were carried out as in the two preceding cases but without glycerol. Acetone was formed in both cases and identified as dinitrophenylhydrazone.

Action of Glycine on Ninhydrin and peri*Naphthindanetrione.*—1 G. of ninhydrin (or 1·3 g. of *peri*naphthindanetrione) in 100 c.c. was placed in a Claisen flask attached to a condenser. Through one opening of the flask, a current of carbon dioxide was bubbled through the solution, and the other opening was provided with a separating funnel containing a solution of 0·4 g. of glycine in 15 c.c. of water. The ninhydrin solution was boiled, and the glycine solution added dropwise. The distillate was collected during 15 minutes, and the formaldehyde formed identified as 2 : 4-dinitrophenylhydrazone (Found, from *peri*naphthindanetrione: C, 40·3; H, 3·9; N, 26·8. Calc. for $C_7H_6O_4N_4$: C, 40·0; H, 2·9; N, 26·7%).

Phenylaminoacetic Acid and 2-Hydroxy-2′-methoxybenzil.—The reaction was carried out in a flask provided with a delivery tube dipping into a solution of phenylhydrazine hydrochloride in aqueous alcohol. The flask, containing the benzil derivative (0·3 g.), phenylaminoacetic acid (0·3 g.), and water (100 c.c.), was put in a thermostat at 37° for 48 hours; the contents of the reaction vessel were then distilled under reduced pressure, the temperature being kept below 37°. The distillate (50 c.c.), which was cooled in ice, was treated with alcoholic phenylhydrazine solution, and benzaldehyde phenylhydrazone (0·2 g.) was formed.

*Dihydroxy*peri*naphthindenone* (III).—*peri*Naphthindanetrione (I) (0·5 g.) and alanine (0·5 g.) were boiled with 200 c.c. of water for 10 minutes in a stream of carbon dioxide; red crystals gradually separated, and the reaction mixture was cooled, and the red compound crystallised from alcohol; it formed red needles, m. p. 255°, proved to be (III) (Errera, *loc. cit.*, p. 583) by m. p., mixed m. p., and comparison of properties; yield almost theoretical (Found: C, 73·5; H, 3·7. Calc. for $C_{13}H_8O_3$: C, 73·6; H, 3·8%).

*Oxidation of Dihydroxy*peri*naphthindenone.*—(a) *By bromine* (cf. Errera, *Gazzetta*, 1913, **43**, I, 353). Bromine-water was added gradually and with shaking to a suspension of 0·5 g. of the red substance in 25 c.c. of warm water till the colour persisted. The reaction mixture was then concentrated and cooled in ice. Yellow crystals were obtained, which proved to be *peri*naphthindanetrione hydrate, by m. p., mixed m. p., and colour reaction with sodium hydroxide.

(b) *By nitric acid.* Nitric acid (5 c.c., *d* 1·1) and water (5 c.c.) were added to a suspension of 0·5 g. of the red substance in 25 c.c. of water. After being heated in a water-bath for 20 minutes the reaction mixture was concentrated. On cooling, yellow crystals of *peri*naphthindanetrione hydrate were obtained and identified as above.

Action of Methylene-blue and Azobenzene on Phenylaminoacetic Acid.—The procedure was the same as in the reaction of *peri*naphthindanetrione and phenylaminoacetic acid, but the triketone was replaced by methylene-blue (1·5 mols.) or azobenzene (1·5 mols.). In neither case was any benzaldehyde obtained. When, however, at the end of either experiment 0·5 g. of ninhydrin in 50 c.c. of water was added to the reaction mixture, a good yield of benzaldehyde was obtained. This proves that the methylene-blue and azobenzene do not react with phenylaminoacetic acid in such a way as to hinder its undergoing the Strecker degradation.

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45. *Preparation of Water-soluble Derivatives of 2-Methylnaphthalene.*

By D. O. HOLLAND and F. A. ROBINSON.

The preparation of several new water-soluble derivatives of 2-methylnaphthalene is described; some of them possess considerable vitamin-K activity.

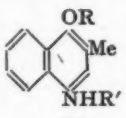
DURING a search for new water-soluble analogues of vitamin K attention has been directed to the preparation of derivatives of 4-amino-2-methyl-1-naphthol (Emmett, Kamm, and Sharp, *J. Biol. Chem.*, 1940, **133**, 285), 1 : 4-diamino-2-methylnaphthalene (Baker and Carlson, *J. Amer. Chem. Soc.*, 1942, **64**, 2658; Veldstra and Wiardi, *Rec. Trav. chim.*, 1942, **61**, 547), and 2-methyl-1 : 4-naphthaquinone 4-monoxime (Dam, Glavind, and Karrer, *Helv. Chim. Acta*, 1940, **23**, 224), all of which possess considerable vitamin-K activity.

Although the hydrochlorides of the two bases are water-soluble, they are not very stable; attempts were therefore made to prepare stable, water-soluble derivatives with similar biological activity. *4-Amino-2-methyl-1-naphthoxyacetic acid* (I; R = $CH_2{\cdot}CO_2H$, R′ = H) was prepared by the series of reactions that Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1917, **39**, 2188) used for the preparation of 4-aminonaphthoxyacetic acid (cf. Howard, *Ber.*, 1897, **30**, 545) from 4-acetamido-2-methyl-1-naphthol and chloroacetic acid.

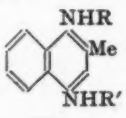
Reaction of the naphthoxy-acid with ethyl chloroacetate in the presence of sodium hydroxide (Jacobs and Heidelberger, *loc. cit.*) yielded *N-4-carboxymethoxy-3-methyl-1-naphthylglycine ethyl ester* (I; R = $CH_2{\cdot}CO_2H$, R′ = $CH_2{\cdot}CO_2Et$); the free acid was unstable in air.

All attempts to prepare the corresponding 4-hydroxy-acid (I; R = H, R′ = $CH_2{\cdot}CO_2H$)

from 4-amino-2-methyl-1-naphthol either by reaction with chloroacetic acid or *via* the cyanide (I; R = H, R′ = CH_2·CN) by reaction with formaldehyde, sodium metabisulphite, and potassium cyanide, were unsuccessful. Since the analogous compound, *p*-hydroxyphenylglycine, can readily be prepared from *p*-aminophenol by both these routes (Meldola, *J.*, 1917, **111**, 552; Galatis, *Helv. Chim. Acta*, 1921, **4**, 574) it would appear that the marked instability of 4-amino-2-methylnaphthol extends to this derivative.



(I.)



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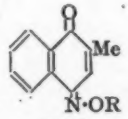

(III.)

Indeed, the preparation of the corresponding N-4-*amino*-3-*methyl*-1-*naphthylglycine* (II; R = H, R′ = CH_2·CO_2H) from 1 : 4-diamino-2-methylnaphthalene, which is more stable than the aminonaphthol, proved to be more successful, although the product was rather unstable. It was synthesised by the method used by Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1917, **39**, 1457) for the preparation of *p*-aminophenylglycine. These workers found that, although the reaction of *p*-aminoacetanilide with chloroacetic acid or its ethyl ester in the presence of bases led mainly to *p*-acetamidophenyldiglycine, the reaction of ethyl chloroacetate with excess of *p*-aminoacetanilide gave the required *p*-acetamidophenylglycine ethyl ester together with *p*-aminoacetanilide hydrochloride. By applying this reaction to the preparation of (II), it has been possible to convert 4-acetamido-3-methyl-1-naphthylamine almost completely into N-4-*acetamido*-3-*methyl*-1-*naphthylglycine ethyl ester* (II; R = Ac, R′ = CH_2·CO_2Et), *N*-4-amino-3-methyl-1-naphthylglycine being obtained on acid hydrolysis. 4-Acetamido-3-methyl-1-naphthylamine was prepared by nitrating 1-acetamido-2-methylnaphthalene (Veselý and Kapp, *Rec. Trav. chim.*, 1925, **44**, 360) and reducing the product catalytically with Raney nickel. The preparation of this compound from 2-methyl-1 : 4-naphthaquinol (Baker and Carlson, *loc. cit.*) was less satisfactory.

Since 2-methyl-1 : 4-naphthaquinol bistrimethylaminoacetate chloride has been shown to possess considerable vitamin-K activity (*idem, ibid.*), the analogous 4-*trimethylaminoacetamido*-2-*methyl*-1-*naphthol chloride* (I; R = H, R′ = CO·CH_2·NMe_3Cl) was prepared. It was synthesised in good yield from 4-*chloroacetamido*-2-*methyl*-1-*naphthol*, obtained by the action of excess of chloroacetyl chloride on the hydrochloride of 4-amino-2-methyl-1-naphthol in the presence of sodium acetate (cf. Jacobs and Heidelberger, *J. Amer. Chem. Soc.*, 1917, **39**, 1442; Rolf, *ibid.*, 1919, **41**, 460), and trimethylamine at room temperature. The corresponding *triethyl chloride* (I; R = H, R′ = CO·CH_2·NEt_3Cl) could be obtained only in very small yield on heating the reactants, but 4-*pyridylacetamido*-2-*methyl*-1-*naphthol chloride* (I; R = H, R′ = CO·CH_2·C_5H_4N,HCl) was formed in good yield under these conditions. These derivatives were readily soluble in water.

Attempts were next made to prepare water-soluble derivatives of 2-methyl-1 : 4-naphthaquinone 4-oxime (III; R = H) similar to those described above. 2-*Methyl*-1 : 4-*naphthaquinone* 4-*carboxymethyl oxime* (III; R = CH_2·CO_2H) was readily prepared by the action of carboxymethoxyamine semihydrochloride (Borek and Clarke, *J. Amer. Chem. Soc.*, 1936, **58**, 2020; Anchel and Schoenheimer, *J. Biol. Chem.* 1936, **114**, 539) on the quinone at pH 3·0, direct action of chloroacetic acid or ester on the quinone oxime in the presence of sodium hydroxide and other bases being unsuccessful.

2-*Methyl*-1 : 4-*naphthaquinone* 4-β-*diethylaminoethyl oxime hydrochloride* (III; R = C_2H_4·NEt_2,HCl) was also readily synthesised from the quinone and β-*diethylaminoethoxyamine* at pH 3·5; it is readily soluble in water. The reagent was prepared by the reaction of acetoxime with β-diethylaminoethyl chloride, followed by acid hydrolysis of the *acetone* β-*diethylaminoethyl oxime* first formed (cf. B.P. 301,956). From the mode of preparation of the last compound and the fact that an electrometric titration with hydrochloric acid revealed the presence of only one basic centre, it would appear to be the required *O*-ether (cf. Thompson and Baer, *J. Amer. Chem. Soc.*, 1940, **62**, 2094; Brady, Dunn, and Goldstein, *J.*, 1926, 2386).

The structure of the two substituted oximes described above was assumed by analogy with the reaction of hydroxylamine with 2-methylnaphthaquinone which is known to give the 4-oxime.

Finally, the *potassium* salt of 2-methyl-1 : 4-naphthaquinone 4-oxime-*O*-sulphonic acid (III; R = SO_3K) was obtained in moderate yield by the action of hydroxylamine-*O*-sulphonic acid (Sommer, Schulz, and Nassau, *Z. anorg. Chem.*, 1925, **147**, 142) on the quinone. The

compound was readily soluble in water and on warming with acid it was quickly converted into the 4-oxime.

A summary of the biological results obtained with some of the compounds described above is given below. The rough sorting test used was carried out on chicks given a vitamin-K-deficient diet for three weeks, a 0·2% concentration of sulphamethazine being added to the drinking water during the last week.

Compound.	Activity.
2-Methyl-1 : 4-naphthaquinone	1·0 (standard)
4-Amino-2-methyl-1-naphthol hydrochloride	0·2
4-Acetamido-2-methyl-1-naphthol	<0·2
4-Acetamido-2-methyl-1-naphthoxyacetic acid	<0·2
4-Amino-2-methyl-1-naphthoxyacetic acid	<0·2
N-4-Carboxymethoxy-3-methyl-1-naphthylglycine ethyl ester	<0·2
N-4-Acetamido-3-methyl-1-naphthylglycine ethyl ester	0·2
N-4-Amino-3-methyl-1-naphthylglycine	0·2
4-Trimethylaminoacetamido-2-methyl-1-naphthol chloride	0·2
2-Methyl-1 : 4-naphthaquinone 4-oxime	0·2
2-Methyl-1 : 4-naphthaquinone 4-carboxymethyl oxime	0·2
Potassium 2-methyl-1 : 4-naphthaquinone-4-oxime-*O*-sulphonate	0·2

Experimental.

All m. p.s are uncorrected.

4-Amino-2-methyl-1-naphthoxyacetic Acid.—4-Amino-2-methyl-1-naphthol hydrochloride was prepared in 55% yield from 2-methyl-1 : 4-naphthaquinone essentially by the method of Sah and Brüll (*Ber.*, 1941, **74**, 552).

To an intimate mixture of finely powdered 4-amino-2-methyl-1-naphthol hydrochloride (10 g.) and fused sodium acetate (5 g.) were added acetic anhydride (5 c.c.) and acetic acid (20 c.c.). The mixture became warm with partial solution of the solid material, and then changed to a solid magma. This was heated on the steam-bath for 1 hr., kept at room temperature for 2 days, and diluted well with water to yield 4-acetamido-2-methyl-1-naphthol as a pink powder (10 g.; 98%); it recrystallised from alcohol (charcoal) as colourless microscopic needles, m. p. 211—212° (Found: C, 72·5; H, 6·1; N, 6·3. Calc. for $C_{13}H_{13}O_2N$: C, 72·5; H, 6·05; N, 6·5%.).

A solution of 4-acetamido-2-methyl-1-naphthol (18·4 g.) and chloroacetic acid (8·1 g.) in water (200 c.c.) containing sodium hydroxide (6·85 g.) was evaporated to *ca.* 75 c.c., further chloroacetic acid (4·0 g.) and sodium hydroxide (3·45 g.) in water (100 c.c.) added, and the mixture reconcentrated to *ca.* 100 c.c. The resulting brown solution was neutralised with dilute hydrochloric acid (Congo-red), and the precipitated solid after being washed with water was recrystallised from alcohol (charcoal) to yield *4-acetamido-2-methyl-1-naphthoxyacetic acid* as a cream-coloured solid, m. p. 208—210° (from 100°) (18 g.; 77%). On recrystallisation from alcohol it formed tiny needles, m. p. 211—211·5° (Found, after drying at 150°: C, 65·5; H, 5·6; N, 5·2. $C_{15}H_{15}O_4N$ requires C, 66·0; H, 5·5; N, 5·1%).

The acetamidonaphthoxyacetic acid (11 g.) was heated under reflux with 15% hydrochloric acid (100 c.c.) for 3 hrs. The clear orange-red solution on cooling deposited a pale pink solid which was washed, dissolved in hot water, and treated with excess of aqueous sodium acetate containing a little sodium hydrosulphite (dithionite), *4-amino-2-methyl-1-naphthoxyacetic acid* separating as a white solid, m. p. 191° (decomp.) (8·6 g.; 86%). It was recrystallised from aqueous alcohol containing sodium dithionite as tiny needles of the same m. p. (Found: C, 67·2; H, 6·0; N, 6·2. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%).

N-*4-Carboxymethoxy-3-methyl-1-naphthylglycine Ethyl Ester.*—A solution of 4-amino-2-methyl-1-naphthoxyacetic acid (10 g.) and ethyl chloroacetate (5·3 g.) in a mixture of N-sodium hydroxide (45 c.c.) and alcohol (50 c.c.) was heated under reflux for 8 hrs. in an atmosphere of nitrogen. An oil separated on cooling which solidified on scratching. This was recrystallised from aqueous alcohol (charcoal), m. p. 137—138° (decomp.) (7·2 g.; 52%) (Found: C, 64·4; H, 6·0; N, 4·4. $C_{17}H_{19}O_5N$ requires C, 64·4; H, 6·0; N, 4·4%).

N-*4-Amino-3-methyl-1-naphthylglycine.*—A solution of 4-acetamido-3-methyl-1-naphthylamine (6·8 g.) and ethyl chloroacetate (2·1 g.) in 50% aqueous alcohol (25 c.c.) was heated under reflux for 5 hrs., the resulting solution cooled in the ice-chest, and the deposited N-*4-acetamido-3-methyl-1-naphthylglycine ethyl ester* (3·9 g.) filtered off, washed with water, and dried, m. p. 188—192°. The filtrate was rendered alkaline with sodium hydrogen carbonate, the solid obtained dissolved in 50% alcohol (20 c.c.), and the solution heated under reflux with fresh ethyl chloroacetate (1·5 c.c.) to yield a further 2·5 g. of the glycine ester. Repetition of the process gave a further quantity of the crude ester (1·0 g.). The combined solids recrystallised from methyl alcohol as colourless needles, m. p. 192—194° (Found: C, 67·6; H, 6·5; N, 9·3. $C_{17}H_{20}O_3N_2$ requires C, 68·0; H, 6·7; N, 9·3%).

The acetamidonaphthylglycine ester (2·2 g.) was heated under reflux for 1 hr. in 15% hydrochloric acid (20 c.c.) in an atmosphere of nitrogen. The resulting solution was concentrated in a vacuum practically to dryness, and the residue dissolved in hot water (*ca.* 150 c.c.). The red solution after the addition of a little sodium dithionite was treated with charcoal to yield an orange solution which was rendered alkaline with sodium acetate. The resulting N-*4-amino-3-methyl-1-naphthylglycine* (0·53 g.) recrystallised from aqueous acetic acid as a light brown powder, m. p. 203—204° (decomp.) (Found: N, 12·2, $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

4-Chloroacetamido-2-methyl-1-naphthol.—To a solution of 4-amino-2-methyl-1-naphthol hydrochloride (25 g.) in a mixture of acetic acid (180 c.c.) and a saturated solution of sodium acetate (180 c.c.), chloroacetyl chloride (25 c.c.) was added dropwise with stirring while the temperature of the mixture

was kept at *ca.* 10°. After the addition, stirring was continued for 1 hr., and then the pink solid was removed and washed well with water (23·5 g.; 79%). The *compound* was recrystallised from aqueous acetic acid containing a little sodium dithionite, forming colourless needles, m. p. 220—221° (decomp.) (Found: C, 62·5; H, 4·8; N, 5·4; Cl, 14·2. $C_{13}H_{12}O_2NCl$ requires C, 62·5; H, 4·8; N, 5·6; Cl, 14·2%).

4-Trimethylaminoacetamido-2-methyl-1-naphthol Chloride.—A suspension of the chloroacetamido-compound (7 g.) in an acetone solution of trimethylamine (100 c.c. of 5%) was shaken for 4 hrs. at room temperature, to yield the quaternary *chloride* as an almost white powder, m. p. 230° (decomp.) (6·65 g.; 77%). It was recrystallised from acetone–methyl alcohol, forming microscopic irregularly shaped crystals, m. p. 232° (decomp.) (Found: C, 62·2; H, 6·8; N, 9·4; Cl, 11·2. $C_{16}H_{21}O_2N_2Cl$ requires C, 62·3; H, 6·8; N, 9·1; Cl, 11·5%).

4-N-Pyridylacetamido-2-methyl-1-naphthol Chloride.—A solution of the chloroacetamido-compound (2 g.) in a mixture of dry pyridine (3 c.c.) and methyl ethyl ketone (20 c.c.) was heated under reflux for 5 hrs., the quaternary *chloride* slowly separating as an orange gum. After removal of the ketone mother-liquor, the gum was heated with a little dry methyl alcohol to yield a pale pink solid, m. p. 260° (decomp.) (2·05 g.; 77·5%). On recrystallisation from acetic acid–ethyl acetate, the compound was obtained as a cream-coloured powder of unchanged m. p. (Found: C, 65·8; H, 5·3; N, 8·0; Cl, 10·8. $C_{18}H_{17}O_2N_2Cl$ requires C, 65·7; H, 5·2; N, 8·5; Cl, 10·8%).

4-Triethylaminoacetamido-2-methyl-1-naphthol Chloride.—A suspension of the chloroacetamido-compound (2 g.) in a mixture of triethylamine (3 c.c.) and acetone (25 c.c.) was heated under reflux for 5 hrs., the solid gradually dissolving. After removal of most of the acetone from the resulting solution, the residue was diluted with water and the solid filtered off. The aqueous filtrate was concentrated in a vacuum to leave an orange oil, which on treatment with hot acetone yielded the quaternary *chloride* as a pale pink powder (0·1 g.). It was recrystallised from methyl alcohol–acetone (charcoal), forming a white powder, m. p. 235° (decomp.) (Found: N, 7·9; Cl, 10·0. $C_{19}H_{27}O_2N_2Cl$ requires N, 8·0; Cl, 10·1%).

2-Methyl-1 : 4-naphthaquinone 4-Carboxymethyl Oxime.—Acetoxime (49 g.) was allowed to react with chloroacetic acid (71 g.) in a solution of sodium hydroxide according to the method of Borek and Clarke (*loc. cit.*), and the resulting crude acetone carboxymethyl oxime (45 g.) hydrolysed by heating under reflux with 3N-hydrochloric acid (450 c.c.) for 1 hr. The hydrolysate was concentrated in a vacuum to *ca.* 60 c.c., treated with 40% sodium hydroxide solution to pH 3·0, and diluted to 120 c.c. Alcohol (120 c.c.) and 2-methyl-1 : 4-naphthaquinone (20 g.) were then added, the mixture heated under reflux for 1 hr., and the resulting brown solution cooled and diluted well with water, crude *2-methyl-1 : 4-naphthaquinone 4-carboxymethyl oxime* separating as a buff-coloured solid. This was dissolved in a warm solution of sodium hydrogen carbonate, the unreacted quinone (1·7 g.) removed, and the filtrate acidified. The precipitated oxime (15 g.; 58%) was recrystallised from alcohol (charcoal), forming pale yellow platelets, m. p. 162° (decomp.) (Found: C, 63·5; H, 4·7; N, 5·7. $C_{13}H_{11}O_4N$ requires C, 63·7; H, 4·5; N, 5·7%).

Acetone β-Diethylaminoethyl Oxime.—To a solution of sodium (9·2 g.) in dry alcohol (300 c.c.) were added acetoxime (14·6 g.) and β-diethylaminoethyl chloride hydrochloride (34·4 g.), and the mixture heated under reflux for 2 hrs. After cooling, the sodium chloride was removed, the orange filtrate acidified with a small excess of hydrochloric acid, and the solution concentrated in a vacuum at low temperature. The resulting syrup was made alkaline with 20% sodium hydroxide solution and the ammoniacal liquid extracted into ether. After removal of solvent, the residue was distilled in a vacuum to give two fractions: (i) b. p. 50—56°/12 mm. (6·1 g.), (ii) b. p. 70—79°/12 mm. (17·4 g.). The main fraction, on redistillation, yielded *acetone β-diethylaminoethyloxime*, b. p. 77—78°/12 mm. (Found: C, 63·3; H, 11·7; N, 16·7. $C_9H_{20}ON_2$ requires C, 62·8; H, 11·6; N, 16·3%). Fraction (i) (Found: C, 62·5; H, 12·4; N, 11·3%) was discarded.

β-Diethylaminoethoxyamine.—Acetone β-diethylaminoethyl oxime (5 g.) was heated under reflux in 3N-hydrochloric acid (50 c.c.) for 1 hr., the solution concentrated in a vacuum, and the resulting yellow syrup made alkaline with sodium hydroxide to yield, after extraction with ether, crude *β-diethylaminoethoxyamine* (4·0 g.). This was distilled under low pressure, b. p. 67—69°/13 mm. (Found: C, 54·8; H, 12·0; N, 20·5. $C_6H_{16}ON_2$ requires C, 54·6; H, 12·1; N, 21·2%). The *hydrochloride*, m. p. 117—119° (slight decomp.), was prepared from a portion of the concentrated syrup, dried in a vacuum at 100° over phosphoric oxide, and the resulting gum crystallised by solution in a small volume of alcohol and precipitation with ether and benzene (Found: C, 35·5; H, 8·8; N, 13·6; Cl, 35·0. $C_6H_{16}ON_2,2HCl$ requires C, 35·5; H, 8·8; N, 13·8; Cl, 35·0%).

2-Methyl-1 : 4-naphthaquinone 4-β Diethylaminoethyl Oxime Hydrochloride.—To a solution of β-diethylaminoethoxyamine (5 g.) in 50% alcohol (60 c.c.) adjusted to pH 3·5 with dilute hydrochloric acid, 2-methylnaphthaquinone (5 g.) was added, and the mixture heated under reflux for 1 hr. The resulting orange-red solution was treated with a little hydrochloric acid and extracted with ethyl acetate which removed a little unreacted quinone (0·5 g.). The aqueous layer was then made strongly alkaline and the yellow oil that separated was extracted into ether. After drying and removal of solvent, the residue (6·25 g.) was heated in a vacuum at 100° to remove unreacted diethylaminoethoxyamine, and the residue diluted with dry ethyl acetate and saturated with hydrogen chloride to yield the required *hydrochloride* as a pale yellow powder; it recrystallised from alcohol–ethyl acetate in the same form, m. p. 179° (decomp) (Found: C, 62·8; H, 7·4; N, 8·9; Cl, 11·0. $C_{17}H_{23}O_2N_2Cl$ requires C, 63·3; H, 7·1; N, 8·7; Cl, 11·0%).

Potassium 2-Methyl-1 : 4-naphthaquinone 4-Oxime-O-sulphonate.—Hydroxylamine-*O*-sulphonic acid (1·14 g.) was dissolved in ice-water (2 c.c.), and the solution diluted carefully with dioxan (10 c.c.), the temperature being kept at 0°. To this mixture were added first a solution of 2-methyl-1 : 4-naphthaquinone (1·72 g.) in dioxan (6 c.c.) and then a 50% aqueous-alcoholic solution of potassium hydroxide (2 c.c. of 14%). The final mixture was left in the ice-chest for 24 hrs. with occasional shaking, and the precipitated solid filtered off, washed with alcohol and ether (1·25 g.), and then extracted with hot alcohol. The required *potassium* salt separated from the alcoholic extract after concentration as very

pale yellow needles, m. p. 158° (decomp.) (0·65 g.; 20%) (Found: C, 40·9; H, 3·4; N, 4·3; S, 9·7. $C_{11}H_8O_5NSK,H_2O$ requires C, 40·9; H, 3·1; N, 4·3; S, 9·9%).

The biological tests were arranged by Mr. M. R. A. Chance in the Biochemical Department of these Laboratories. We wish to express our thanks to him, to Mr. B. Brown for help in the other experimental work, and to Mr. A. L. Bacharach for making this assistance available to us.

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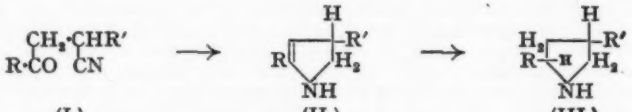
46. β-*Cycloylpropionitriles. Part III. Reduction to 2-Cyclyl-Δ²-pyrrolines and 2-Cyclylpyrrolidines.*

By EDWARD B. KNOTT.

β-Cycloylpropionitriles are reduced catalytically to 2-cyclyl-Δ²-pyrrolines and 2-cyclylpyrrolidines. α-Carboxy-β-benzoylpropionitrile on reduction gives poor yields of two amino-acids and by a peculiar reaction a 17% yield of 2-phenylpyrrole.

THE conversion of β-cycloylpropionitriles (I) into pyrrole dyes has been described in Parts I and II but hitherto no simple pyrrole derivative has been obtained. By the catalytic reduction of (I) using Raney nickel, simple 2-cyclyl-Δ²-pyrrolines (II) and 2-cyclylpyrrolidines (III) have now been obtained in good yield. This preparation of monosubstituted reduced pyrrole ring systems is analogous to the formation of disubstituted analogues by the reduction of β-aroyl-α-



(I.) (II.) (III.)

arylpropionitriles (I; R, R′ = aryl) described by Rogers (*J.*, 1943, 594) who used the same catalyst (see also Rupe and Gisiger, *Helv. Chim. Acta*, 1925, **8**, 338). The reaction as far as the pyrroline proceeds rapidly at room pressure and temperature (23°) but the further reduction to the pyrrolidine is a lengthy procedure under like conditions.

A remarkable property of the pyrrolines and pyrrolidines is the great change in their odour given by small changes in the groups at the 2-positions.

The preparation of 2-cyclylpyrrolines and -pyrrolidines from the corresponding cyclyl methyl ketones is thus readily achieved by this method.*

An attempted selenium dehydrogenation of 2-phenylpyrroline did not give the required 2-phenylpyrrole; the main product was an unstable solid fluorescing strongly in alcoholic solution from which selenium separated on standing.

It was thought to be of interest to determine whether substances of type (II; R′ = H) could be obtained by catalytic reduction of α-cyano-β-aroylpropionic acids (I; R′ = CO_2H) followed by decarboxylation. This alternative synthesis would be attractive since (I; R′ = CO_2H) is readily obtained by the Friedel–Crafts condensation of the carbocycle or heterocycle with maleic anhydride to the substituted acrylic acid followed by hydrogen cyanide addition.

Reduction of the acid was rapid under conditions similar to the reduction of the nitrile. However, owing to the release of carbon dioxide during hydrogenation, the apparent volume of hydrogen absorbed was only half that required to give a pyrroline. Small yields of two amino-acids were obtained, however, the analysis of one indicating its being *4-carboxy-2-phenyl-Δ²-pyrroline* (II; R = Ph, R′ = CO_2H); that of the other was indeterminate. Somewhat larger yields of 2-phenylpyrrole, however, were isolated (16—17%). The formation of this substance is surprising and must occur either through disproportionation of the pyrroline, or by direct loss of formic acid from the carboxypyrroline. A more careful examination of the hydrogenation products should clear that point.

* Since this work was completed a publication by Dhont and Wibaut (*Rec. Trav. chim.*, 1944, **63**, 8) has appeared. These authors obtained 2-*p*-chlorophenyl-Δ²-pyrroline as its picrate by the zinc and hydrochloric acid reduction of *p*-chloro-α-nitrobutyrophenone. The latter was obtained by the conversion of *p*-chloroacetophenone into the Mannich base, followed by distillation to the vinyl ketone, then nitromethane addition.

Experimental.

(Microanalyses are by Drs. Weiler and Strauss, Oxford; m. p.s are uncorrected.)

2-Phenyl-Δ²-pyrroline (II; R = Ph).—β-Benzoylpropionitrile (31·8 g., 0·2 mol.), dissolved in methyl alcohol (300 c.c.), was shaken with Raney nickel (5 g.) at room temperature and pressure. After the absorption of hydrogen (0·4 mol.) had been completed, the catalyst was filtered off and the alcohol distilled. The greenish oil had b. p. 252°/760 mm. and weighed 25 g. (86%). It crystallised on standing and formed large plates, m. p. 46°, from light petroleum (Gabriel and Colman, *Ber.*, 1908, **41**, 517, give m. p. 44—45°) (Found: C, 82·3; H, 7·5; N, 9·55. Calc. for $C_{10}H_{11}N$: C, 82·25; H, 7·55; N, 9·6%). The *picrate* formed yellow blades, m. p. 198°, from ethyl alcohol (Found: N, 15·1. $C_{16}H_{14}O_7N_4$ requires N, 15·0%). It was further characterised by shaking with benzoyl chloride and aqueous sodium hydroxide according to the directions of Gabriel *et al.* (*loc. cit.*), giving γ-benzamidobutyrophenone m. p. 125—126° (Found: N, 5·3. Calc. for $C_{16}H_{15}O_2N$: N, 5·55%).

2-Phenylpyrrolidine (III; R = Ph).—β-Benzoylpropionitrile (7·95 g., 0·05 mol.) was reduced in presence of Raney nickel (2 g.) and methyl alcohol (100 c.c.) by shaking with hydrogen until 0·15 mol. was absorbed. The last 0·05 mol. was absorbed slowly. Removal of the alcohol left an oil (5·7 g., 77·5%), b. p. 239°/756 mm. (Gabriel and Colman, *loc. cit.*, give b. p. 241°/771 mm.) (Found: N, 9·55. Calc. for $C_{10}H_{13}N$: N, 9·55%); *picrate*, m. p. 149° (lit. m. p. 148—149°) (Found: N, 15·1. Calc. for $C_{16}H_{16}O_7N_4$: N, 14·9%).

2-p-Tolyl-Δ²-pyrroline (II; R = *p*-Me·C_6H_4).—β-*p*-Toluoylpropionitrile, reduced as for the benzoyl analogue, gave a crystalline solid (6·3 g., 79·5%) forming cream aggregates, m. p. 65°, from light petroleum. It had a peculiar caraway odour when heated alone or in water (Found: N, 8·75. $C_{11}H_{13}N$ requires N, 8·5%). Its *picrate* was obtained as irregular plates, m. p. 184°, from spirit (Found: N, 14·1. $C_{17}H_{16}O_7N_4$ requires N, 14·4%).

2-p-Tolylpyrrolidine (III; R = *p*-Me·C_6H_4), obtained analogously, formed a colourless oil, b. p. 354—356°/755 mm., with an odour similar to that of the phenyl analogue (Found: N, 8·75. $C_{11}H_{15}N$ requires N, 8·7%). Its *picrate* formed large, yellow plates, m. p. 170—172°, from alcohol (Found: N, 14·2. $C_{17}H_{18}O_7N_4$ requires N, 14·35%).

2-p-Anisyl-Δ²-pyrroline (II; R = *p*-MeO·C_6H_4).—This was obtained analogously in 89% yield by reducing β-4-methoxybenzoylpropionitrile. It was obtained as glistening, pale yellow plates, m. p. 74°, from light petroleum. After repeated recrystallisation it had m. p. 69°. It possesses a pleasant odour not unlike that of piperonal (Found: N, 7·7. $C_{11}H_{13}ON$ requires N, 8·0%). Its *picrate* formed flat yellow needles, m. p. 175°, softening at 171°, from alcohol (Found: N, 13·9. $C_{17}H_{16}O_8N_4$ requires N, 13·85%).

2-p-Anisylpyrrolidine (III; R = *p*-MeO·C_6H_4).—The nitrile absorbed the third hydrogen molecule very slowly (2 days) even with a large amount of nickel. It formed a colourless oil, b. p. 284°/760 mm., in 78% yield. It possesses a peculiar fishy odour (Found: N, 7·8. $C_{11}H_{15}ON$ requires N, 7·9%). Its *picrate* was obtained as yellow needles, m. p. 172—173°, from alcohol (Found: N, 14·2. $C_{17}H_{18}O_8N_4$ requires N, 13·8%).

2-m-Hydroxyphenyl-Δ²-pyrroline (II; R = *m*-HO·C_6H_4).—Hydrogenation of β-3-hydroxybenzoylpropionitrile with subsequent filtration and removal of alcohol gave a solid which on dissolving in hot methyl alcohol gave an intensely blue solution. It is recrystallised preferably from benzene since no blue colour develops in this solvent. It was thus obtained as colourless needles, m. p. 156°, containing solvent lost on exposure to the atmosphere (Found: N, 8·7. $C_{10}H_{11}ON$ requires N, 8·7%). Its *picrate*, unlike others of this series, crystallised very slowly on adding alcoholic picric acid to the alcoholic solution of the base. It formed needles, m. p. 197—199°, from spirit (Found: N, 14·0. $C_{16}H_{14}O_8N_4$ requires N, 14·35%).

In an attempt to prepare the pyrrolidine, the nitrile was shaken to absorb 3 mols. of hydrogen, and the alcohol removed. A resin, soluble in alkali or acid, was obtained, which, however, could not be distilled, and formed an oily picrate.

2-(2′-Naphthyl)-Δ²-pyrroline (II; R = 2-$C_{10}H_7$).—This was obtained, in 82% yield, on reducing β-2-naphthoylpropionitrile, as almost colourless needles, m. p. 96°, from light petroleum. It had an odour not unlike that of quinoline (Found: N, 7·45. $C_{14}H_{13}N$ requires N, 7·2%). Its *picrate* formed jagged needles, m. p. 182°, from spirit (Found: N, 13·7. $C_{20}H_{16}O_7N_4$ requires N, 13·2%).

2-(3′:4′-Dimethoxyphenyl)-Δ²-pyrroline.—β-3:4-Dimethoxybenzoylpropionitrile (4·38 g.) was reduced in presence of Raney nickel (1 g.) and methyl alcohol (50 c.c.) to give the *pyrroline* in 88% yield, which was obtained as colourless needles, m. p. 77—79°, from benzene–light petroleum (Found: N, 6·95. $C_{12}H_{15}O_2N$ requires N, 6·85%). Its vapour had a peculiar, sharp odour. Its picrate formed flat needles, m. p. 205—207°, from spirit (Found: N, 13·0. $C_{18}H_{18}O_9N_4$ requires N, 12·9%).

2-(3′:4′-Dimethoxyphenyl)pyrrolidine.—This *base* was obtained as a thick oil, b. p. 289—291°/758 mm., with a strong odour of bloaters (Found: N, 6·8. $C_{12}H_{17}O_2N$ requires N, 6·75%). Its *picrate* formed needles, m. p. 200° (previous softening), from ethyl alcohol (Found: N, 13·2. $C_{18}H_{20}O_9N_4$ requires N, 12·85%).

2-p-Chlorophenyl-Δ²-pyrroline (II; R = *p*-Cl·C_6H_4).—β-*p*-Chlorobenzoylpropionitrile (3·87 g.), methyl alcohol (50 c.c.) and Raney nickel (1 g.) were shaken to absorb hydrogen (0·04 mol.). The nickel was filtered off, the alcohol removed, and the solid residue dissolved in light petroleum (100 c.c.), filtered to remove a cloudiness, and concentrated to 10 c.c. The *pyrroline* crystallised as pale green needles. Further concentration gave a second crop, 3·1 g. in all (86%). It formed colourless glassy needles, m. p. 67°, from light petroleum. It had a strong minty odour, particularly on heating (Found: N, 7·75. $C_{10}H_{10}NCl$ requires N, 7·8%). Its picrate formed irregular plates, m. p. 209—210°, from spirit (Dhont and Wibaut, *Rec. Trav. chim.*, 1944, **63**, 81, give m. p. 210—211°. They did not isolate the base) (Found: N, 14·2. Calc. for $C_{16}H_{13}O_7N_4Cl$: N, 13·7%).

2-(2′-Thienyl)-Δ²-pyrroline (II; R = 2-C_4H_3S).—β-2-Thienoylpropionitrile was reduced as for the benzoyl analogue. Removal of the solvent left an oil with an odour not unlike that of quinoline. It was

fractionally distilled under 750 mm., and the fractions b. p. 250—255° and 255—265° collected. The lower-boiling fraction solidified completely, and the other partly crystallised after inoculation. From light petroleum the *pyrroline* (26·5%) formed long flat needles, m. p. 59° (Found: N, 9·4; S, 21·2. C_8H_8NS requires N, 9·25; S, 21·2%). Its *picrate*, m. p. 195—197°, formed long, flat needles from alcohol (Found: N, 14·3. $C_{14}H_{12}O_7N_4S$ requires N, 14·75%).

2-(2′-*Furyl*)-Δ^2-*pyrroline* (II; R = 2-C_4H_3O).—Removal of the solvent after the reduction of β-2-furoylpropionitrile left an oil which crystallised. It was dissolved in dilute hydrochloric acid, giving a bright yellow solution of the salt, filtered from a little tar, made alkaline with solid sodium carbonate, and the water-soluble base extracted with ether. After drying, the ether was removed, leaving the base, which crystallised. It tended to crystallise with a sticky impurity so it was converted into its *picrate* forming flat needles, m. p. 175—177°, from ethanol (Found: N, 15·3. $C_{14}H_{12}O_8N_4$ requires N, 15·4%). The *base*, released by conversion into its hydrochloride followed by basifying the aqueous solution of the latter, and extraction with ether as above, was then obtained pure as tiny, flat, pale yellow needles, m. p. 55—56°, from light petroleum, with an odour of thiazole (Found: N, 10·3. C_8H_9ON requires N, 10·3%).

2-(2′-*Coumaronyl*)-Δ^2-*pyrroline*.—2-Coumaronyl β-cyanoethyl ketone was reduced to give an oil which crystallised. It tended to crystallise from light petroleum with a sticky contamination so it was converted into its *picrate*, m. p. 192—194°, obtained as tiny glistening plates from 95% alcohol (Found: N, 13·25. $C_{18}H_{14}O_8N_4$ requires N, 13·5%). The *base* regenerated from the picrate formed tiny, cream needle rosettes, m. p. 97—99°, from light petroleum. Its vapour (in steam) has a pleasant aromatic odour (Found: N, 7·75. $C_{12}H_{11}ON$ requires N, 7·55%).

Attempted Selenium Dehydrogenation of 2-Phenyl-Δ^2*-pyrroline*.—The pyrroline (5 g.) and selenium (5 g.) were refluxed gently for 3 hours. The reddish liquor partly solidified. It was extracted three times with boiling ligroin, leaving a buff powder (2 g.), which fluoresced strongly in methyl alcohol solution, but was unstable and deposited selenium on attempted crystallisation. The ligroin extract gave a little crystalline solid contaminated with a resinous oil on concentration. Neither solid was investigated further.

Catalytic Reduction of α-Cyano-β-benzoylpropionic Acid.—The acid hydrate (22·1 g., 0·1 mol.), methyl alcohol (50 c.c.), and Raney nickel (5 g.) were shaken to absorb hydrogen. Owing to carbon dioxide evolution the amount of hydrogen absorbed was unknown, but after a volume had been absorbed corresponding to 0·2 mol. of hydrogen the absorption became slow and a solid separated. The nickel and solid (A) were filtered off, and the filtrate (B) left overnight. The solid (A) was dissolved in 2N-sodium carbonate, the solution filtered, and the *acid* (II; R = Ph, R′ = CO_2H) reprecipitated with acetic acid. It formed colourless grains, m. p. 192—193°, from methyl alcohol (Found: C, 71·65; H, 5·45; N, 7·4. $C_{11}H_{11}O_3N$ requires C, 69·8, H, 5·85; N, 7·4%).

The filtrate (B) deposited a further crop of (A) on standing (1·2 g.). The methyl alcohol was distilled off, and the residue extracted twice with boiling benzene. The residue consisted chiefly of (A) but was difficult to purify. The benzene extract deposited a mass of crystals on cooling. They (2 g.) formed bundles of asbestos-like needles, m. p. 140°, from methyl alcohol, soluble in acid and alkali (Found: C, 67·55; H, 5·3; N, 6·45%).

The benzene filtrate was distilled to remove the benzene, and the residue extracted repeatedly with ligroin to give 2-phenylpyrrole (2·4 g., 16·8%), m. p. 129°, mixed m. p. with authentic specimen 129° (Found: N, 9·85. Calc. for $C_{10}H_9N$: N, 9·8%).

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47. *Potential Trypanocides of the N-Heterocyclic Series. Part I. Phenanthridinium Salts.*

By A. G. CALDWELL and L. P. WALLS.

The powerful trypanocidal properties of aminophenanthridinium salts suggested that further isomerides should be prepared. Those with 2- (I; R = R″ = NH_2, R′ = H) and 6- and 8- (II; R = R′ = NH_2) amino-substituents were of particular interest because of the possibilities of ionic resonance. For the synthesis of the former, 2-nitrobenzidine was converted by a number of stages into 2-acylamido-4-carbethoxyaminodiphenyls (IV; R = Me and *p*-C_6H_4·NO_2), which were cyclised to the corresponding phenanthridines (V). For the 6- and 8-amino-compounds acyl derivatives of 2-*amino*-3′-*carbethoxyaminodiphenyl* (VII) were similarly cyclised, the quantitative yields illustrating the favourable influence of the urethane group on this type of ring-closure. The acetamido-compound gave a high yield of the 6-isomeride with some 8-isomeride (VIII), but the *p*-nitrobenzamido-compound gave a higher yield of 8-isomeride. An explanation is offered for this phenomenon. Quaternary salts of these new series were prepared in the usual way.

Compounds of similar structure with a 9-*p*-aminobenzyl substituent (XIII; R = R′ = NH_2) were also synthesised. Salts of this series in which R = NO_2 were readily converted into anhydro-bases (XIV).

The fact that the acetamido- is much more readily hydrolysed than is the carbethoxyamino-group was advantageously used in the preparation of intermediates, and also for the synthesis of quaternary salts containing an amino-group in the phenanthridine part of the molecule and a carbethoxyamino-group in the 9-substituent. Thus (I; R = NH·CO_2Et, R′ = NH_2,

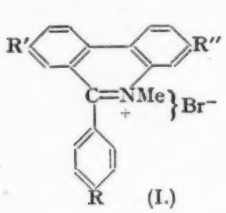
R″ = H), (I; R = NH·CO_2Et, R″ = NH_2, R′ = H), and (XIII; R = NH·CO_2Et, R′ = NH_2) were prepared.

The quaternary salts generally have a powerful *in vitro* antibacterial action not reduced in the presence of blood. Several salts show a chemotherapeutic action in streptococcal infections of mice, and some, particularly (I; R = R″ = NH_2, R′ = H) and (II; R = R′ = NH_2) are powerfully active in *T. congolense* infections in mice.

It is well known that certain important trypanocides, particularly those effective against the monomorphic trypanosomes and *T. cruzi*, are to be found among *N*-heterocyclic compounds. Previous work has shown that quaternary phenanthridine salts with free amino-groups are not only highly antibacterial *in vitro*, but exert a curative action in trypanosome infections in animals, particularly those due to the bovine parasites *T. congolense* and *T. vivax* (Browning, Browning, and Robb, *J. Path. Bact.*, 1940, **50**, 371). The trypanocidal activity is greatest in 9-phenylphenanthridinium salts containing two amino-groups, and as far as published work shows reaches a maximum in 2 : 7-diamino-9-phenyl-10-methylphenanthridinium bromide (I; R′ = R″ = NH_2, R = H; " phenanthridinium 1553 ", " dimidium bromide "). High trypanocidal activity is also present when one of the amino-groups is situated in the 9-phenyl substituent (as I; R = R′ = NH_2, R″ = H; " phenanthridinium 897 ", " phenidium chloride "). It would appear that the 7-amino-group is particularly associated with trypanocidal action, for the corresponding 3-amino-compounds are less effective, but it was clearly desirable to examine compounds of the same type with the amino-groups in other positions. The high activity of (I; R′ = R″ = NH_2, R = H) and (I; R = R′ = NH_2, R″ = H) suggested that the third member of the triad (I; R = R″ = NH_2, R′ = H) was particularly worthy of investigation. In the latter both amino-groups are capable of ionic resonance with the heterocyclic *N*-atom, whereas only one amino-group in either of the former compounds is thus suitably placed. Recently suggestions have been made that ionic resonance of the same type may be associated with parasiticidal properties (see *inter alia*, Kumler and Daniels, *J. Amer. Chem. Soc.*, 1943, **65**, 2190), and it was of interest to assess trypanocidal activity in this series from that point of view. Similar compounds containing 6- or 8-amino-groups (cf. II; R = R′ = NH_2) would likewise possess two amino-groups capable of ionic resonance. The preparation of these phenanthridinium compounds with 2-, 6-, or 8-amino-groups has been accomplished by using the method recently reported (Walls, *J.*, 1947, 67) of cyclising *o*-acylamidodiphenyls containing urethane substituents.

The 2 : 4-disubstituted diphenyls required for the synthesis of 2-aminophenanthridines are not readily available. Gull and Turner (*J.*, 1929, 496) obtained 2 : 4-dinitrodiphenyl by a " mixed " Ullmann reaction and Finzi and Bellavita (*Gazzetta*, 1938, **68**, 78) the same compound in two stages from 2-nitro-4′-aminodiphenyl, but neither method appeared to offer a good route to the phenanthridines. For this purpose a more promising starting material was 2-nitrobenzidine, from which Cain and May (*J.*, 1910, **97**, 724) obtained a substance in high yield, m. p. 186—187°, by monoacetylation. They stated that this product was 2-nitro-4-amino-4′-acetamidodiphenyl, and repetition of their work has shown that this is indeed the chief product, having m. p. 210°, but some diacetyl compound is also formed. Conversion of this monoacetyl compound into *2-nitro-4-carbethoxyamino-4′-acetamidodiphenyl* (III; R = NH·COMe) is quantitative, and by taking advantage of the marked resistance of the urethane group to acid hydrolysis, this substance may be converted into *2-nitro-4′-amino-4-carbethoxyaminodiphenyl* (III; R = NH_2). The same method of partial hydrolysis may be employed for the preparation of the useful intermediate 2-amino-4′-carbethoxyaminodiphenyl (Walls, *loc. cit.*), which is thus obtained quantitatively by hydrolysis of the readily accessible acetyl compound. The diazotisation of (III; R = NH_2) and subsequent elimination of the diazonium group to give 2-nitro-4-carbethoxyaminodiphenyl (III; R = H) presented considerable difficulty owing to the extremely sparing solubility of the salts of the amine, and of the diazonium salts. The best results were obtained when the diazonium sulphate was decomposed in aqueous alcohol by hypophosphorous acid, a complex reaction in which considerable quantities of acetaldehyde were formed. The constitution of the product was confirmed by hydrolysis of the urethane group to furnish *2-nitro-4-aminodiphenyl*, thus incidentally confirming by the difference of this substance from 2-nitro-4′-aminodiphenyl, the constitution allotted by Cain and May (*loc. cit.*) to monoacetyl-2-nitrobenzidine. Reduction of (III; R = H) furnished an amine not yet obtained crystalline, of which the appropriate *acyl* derivatives (IV) were smoothly cyclised to the *phenanthridines* (V; R = Me) and (V; R = *p*-C_6H_4·NO_2). From these products the corresponding *amines* were obtained by hydrolysis. 2-Carbethoxyamino-9-methylphenanthridine (V; R = Me) was converted into the quaternary *salt*, which was hydrolysed to the red *amino*-salt (VI). The quaternary *salt* from 2-carbethoxyamino-9-*p*-nitrophenylphen-

anthridine (V; R = *p*-C_6H_4·NO_2) was hydrolysed to the purple-black *nitro-amino*-salt (I; R = NO_2, R″ = NH_2, R′ = H), reduction of which with iron powder yielded the required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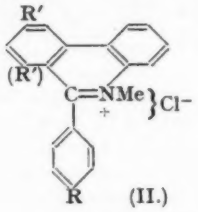
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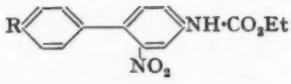
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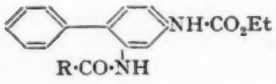
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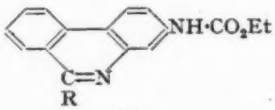
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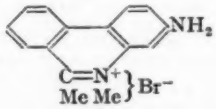
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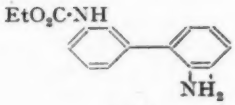
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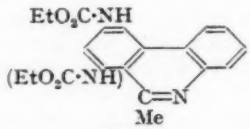
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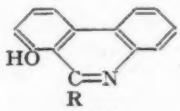
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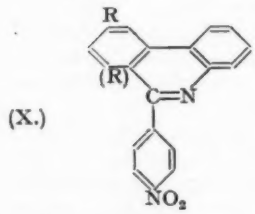
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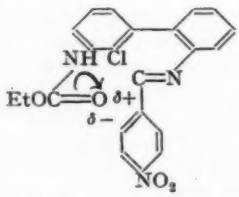
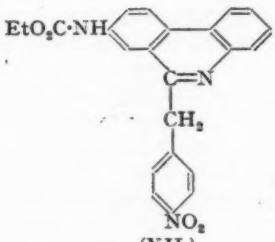

(XI.)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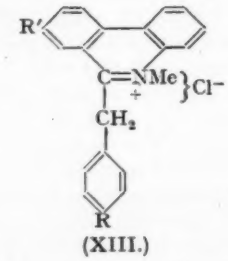
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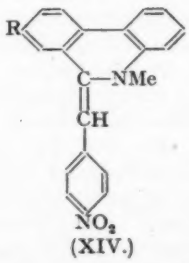
(XIV.)

diamino-salt (I; R = R″ = NH_2, R′ = H) accompanied by a sparingly soluble by-product. The properties of the salts of this series are very similar to those of the corresponding 7-series (Walls, *loc. cit.*).

For the preparation of (II; R = R′ = NH_2) 2 : 3′-dinitrodiphenyl was reduced to 2-nitro-3′-aminodiphenyl by a modification of the method due to Case (*J. Amer. Chem. Soc.*, **1939**, **61**, 767). Successive carbethoxylation and reduction afforded 2-*amino*-3′-*carbethoxyamino-diphenyl* (VII). The *acetyl* derivative of (VII) was rapidly and quantitatively converted by phosphoryl chloride into a mixture of 6- and 8-*carbethoxyamino*-9-*methylphenanthridines* (VIII), this facile reaction illustrating again the favourable effect on this type of ring-closure of the urethane group, for which it may be assumed that the (+*M*) compensates for the (−*I*) effect. The isomerides were separated by crystallisation of their sulphates, and that formed in small amount was converted into the *hydroxyl* compound (IX; R = Me), which gave a strong Gibbs's indophenol reaction thus indicating the presence of a free *p*-position to the hydroxyl group. Consequently it was the 8-isomeride, and the ring-closure had yielded a preponderant amount of the 6-isomeride, as would be expected on account of both the mesomeric and the steric effects of the urethane group. A series of quaternary salts was prepared from this isomeride.

Ring-closure of the p-*nitrobenzamido*-derivative of (VII) was also almost quantitative but

presented different features from that of the acetyl compound. Again two products were isolated, one sparingly soluble substance, m. p. 250°, in 35% yield, and a much more soluble substance, m. p. 200°, in 45% yield. By hydrolysis of the latter and diazotisation of the resulting amine, an alkali-insoluble *hydroxyl* compound (IX; R = p-C_6H_4·NO_2) was obtained which gave a positive Gibbs's reaction; the isomeric *hydroxyl* compound was soluble in alkali and gave a negative reaction. Thus the more soluble derivative is 8-*carbethoxyamino*-9-p-*nitrophenylphenanthridine* (cf. X; R = NH·CO_2Et), and a ring-closure $o : p$ ratio >1 obtains. A tentative explanation of the markedly different $o : p$ ratios for the acetamido- and p-nitrobenzamido-compounds is that in the latter the powerful electron-attraction effect of the nitro-group greatly increases the " positivity " of the carbon atom of the iminochloride assumed to be an intermediate in ring closure [see (XI)]. Then electrostatic attraction might be possible between this carbon atom and the carbonyl oxygen of the urethane group. Such an interaction would favour formation of the 8-isomeride. Both isomerides were converted into quaternary *salts* (II; R = NO_2, R′ = NH·CO_2Et), the 8-isomeride giving a poor yield, attributable to steric hindrance by the urethane group, which is seen in models to come into close contact with the heterocyclic nitrogen atom in one phase of its rotation. These quaternary salts were hydrolysed to the *nitro-amino*-salts (II; R = NO_2, R′ = NH_2), from which the *diamino*-salts (II; R = R′ = NH_2) were obtained by reduction. The salts of the 8-series were more soluble and much more deeply coloured than those of the 6-series; thus (II; R = NO_2, R′ = NH·CO_2Et) are orange and pale yellow respectively (II; R = NO_2, R′ = NH_2) purple and light brown, and (II; R = R′ = NH_2) light red and yellow. The light-absorption properties of these compounds are being examined.

The foregoing experiments were designed to test whether ionic resonance is a necessary feature in trypanocidal compounds of this series. To this end also it was decided to modify the active type (I; R = R′ = NH_2, R″ = H) so that ionic resonance becomes impossible. For this purpose the p-*aminobenzyl* salts (XIII; R = R′ = NH_2) were chosen. 4-*Carbethoxyamino*-2′-p-*nitrophenylacetamidodiphenyl* was readily cyclised to the corresponding *phenanthridine* (XII), which was converted into a series of quaternary salts. The salts (XIII; R = NO_2, R′ = NH·CO_2Et) and (XIII; R = NO_2, R′ = NH·COMe) had the property not possessed by salts of the 9-p-nitrophenyl series of being converted by warm water into deep-coloured substances, the effect being reversed by dilute acid. With alkali similar substances were precipitated. They are readily soluble in ether or benzene and are undoubtedly anhydro-bases (XIV), similar to the compound obtained by Koenigs, Kohler, and Blindow (*Ber.*, 1925, **58**, 933) from 2-p-nitrobenzylpyridinium salts. As suggested by these authors the effect is to be ascribed to the powerful electron-attracting effect of the nitro-group, since salts of this series not possessing a nitro-substituent in the 9-benzyl group behave normally with alkali to give lightly-coloured pseudo-bases. Similar phenomena were observed with 9-p-*nitrobenzyl*-10-*methylphenanthridinium chloride* (XIII; R = NO_2, R′ = H).

In a discussion of the relationship between trypanocidal action and structure in this series, Browning, Calver, and Leckie point out (*J.*, 1947, 69) that a high degree of activity is retained when the amino-group R in (I; R = R′ = NH_2, R″ = H) is replaced by a nitro-group. In view of the effect of the urethane group on therapeutic properties (Browning, Calver, Leckie, and Walls, *Nature*, 1946, **157**, 263) it was of interest to investigate active types in which R = NH·CO_2Et. 7-*Amino*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (as I; R = NH·CO_2Et, R′ = NH_2) was readily obtained by hydrolysis of the acetyl compound (Walls, *loc. cit.*) with dilute hydrochloric acid, and by a similar application of the method of partial hydrolysis (I; R = NH·CO_2Et, R″ = NH_2, R′ = H) and (XIII; R = NH·CO_2Et, R′ = NH_2) were prepared.

Compounds described in this paper have been examined by Dr. Brownlee and his colleagues at the Wellcome Physiological Research Laboratories for antibacterial properties. The quaternary salts have generally a high bacteriostatic action *in vitro* particularly against Gram-positive organisms, an effect which is not reduced by the presence of blood. Of these some afford protection against a number of lethal doses of *Streptococcus pyogenes* in mice, (VI) being the most effective in this respect. Mr. Goodwin and his colleagues at the Wellcome Laboratories of Tropical Medicine have shown that many of these salts are trypanocidal particularly against *T. congolense* in mice infections. The third member of the triad (I; R = R″ = NH_2, R′ = H) has a very powerful action as has also [II; R = R′ = NH_2 (6-isomer)], but it may be said that no convincing correlation between ionic resonance and trypanocidal action has yet been found. Full details of these and other interesting pharmacological properties will be published elsewhere.

Experimental.

2-Nitro-4-amino-4'-acetamidodiphenyl.—To a solution of 2-nitrobenzidine (40 g.) in boiling alcohol (360 ml.) was added hot water (360 ml. at 60°) and acetic anhydride (17 ml.). The solution was refluxed for 10 minutes, and then treated with cold water (360 ml.) and allowed to cool. The mixture (*ca.* 40 g.) of mono- and di-acetyl compounds that crystallised was dissolved in boiling acetone (500 ml.), most of the diacetyl compound (*ca.* 5 g.) remaining undissolved. Acetone was removed from the filtrate by distillation; the residue crystallised from alcohol in golden yellow plates of the monoacetyl compound (*ca.* 25 mg.), m. p. 210° (Found: C, 62·0; H, 4·85; N, 15·55. Calc. for $C_{14}H_{13}O_3N_3$: C, 61·95; H, 4·85; N, 15·5%).

2-Nitro-4-carbethoxyamino-4'-acetamidodiphenyl (III; R = NH·COMe).—The foregoing mono-acetyl compound (20 g.) was dissolved in boiling alcohol (250 ml.) and treated with diethylaniline (16 ml.) and then dropwise with ethyl chloroformate (8 ml.). After the vigorous reaction had subsided the solution was refluxed for 10 minutes, filtered (charcoal) from any diacetyl compound present as impurity in the starting-material, and allowed to cool. The *urethane* crystallised in yellow prisms (21 g.), which melted *ca.* 218° (efferv.) and then resolidified (Found: C, 59·85; H, 5·3; N, 12·25. $C_{17}H_{17}O_5N_3$ requires C, 59·45; H, 5·0; N, 12·25%).

2-Nitro-4'-amino-4-carbethoxyaminodiphenyl (III; R = NH_2).—The foregoing urethane (20 g.) was refluxed for 2½ hours in alcohol (270 ml.) and concentrated hydrochloric acid (30 ml.), yellow prismatic crystals of the hydrochloride of the *product* beginning to separate after about 2 hours. Dilution of the hot reaction mixture with water and neutralisation with alkali precipitated a yellowish-brown crystalline base (16·5 g.), which on recrystallisation from alcohol gave prisms, varying in colour from yellow to brown in different preparations (12·5 g.), m. p. 177° (Found: C, 59·85; H, 5·15; N, 13·9. $C_{15}H_{15}O_4N_3$ requires C, 59·8; H, 5·05; N, 13·95%). This amine formed extremely sparingly soluble salts with aqueous hydrochloric and sulphuric acids.

2-Nitro-4-carbethoxyaminodiphenyl (III; R = H).—The following method generally gave good results, although occasionally poor yields were inexplicably obtained. The amine (20 g.) was dissolved in boiling alcohol (600 ml.), the solution cooled to 40°, and treated with stirring with concentrated sulphuric acid (10 ml.). A sparingly soluble sulphate was precipitated by the first additions of acid, but finally redissolved. The solution was cooled rapidly to 20°, and, before an acid sulphate crystallised, sodium nitrite (7 g.) in water (120 ml.) was added with stirring; after 10 minutes hypophosphorous acid (40 ml. of *ca.* 30%) was added and stirring continued for 4 hours, a strong odour of acetaldehyde being observed. Addition of water precipitated the crude product in flocculent crystals, which were extracted with benzene, some sticky impurity remaining undissolved. The extract was washed successively with sodium hydroxide solution, water, dilute sulphuric acid, and water, and finally dried (Na_2SO_4). On evaporation of benzene the product was obtained as a brown crystalline mass. To obtain the pure substance the benzene solution was filtered through a column of alumina, impurities being strongly adsorbed. By evaporation of the yellow benzene eluate the *product* was obtained in feathery yellow needles (15 g.), m. p. 123° (Found: C, 63·5; H, 4·65; N, 9·85. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9; N, 9·8%). A solution of this nitro-compound (1 g.) in sulphuric acid (4 ml. of concentrated acid and 2 ml. of water) was heated to 125°. Rapid effervescence occurred with darkening in colour and after 15 minutes the solution was cooled and diluted with water; white crystals of a sulphate separated, from which *2-nitro-4-aminodiphenyl* was liberated by alkali; it crystallised from aqueous alcohol in golden yellow plates, m. p. 109·5° (Found: C, 67·25; H, 4·8; N, 13·1. $C_{12}H_{10}O_2N_2$ requires C, 67·25; H, 4·7; N, 13·1%).

2-Acetamido-4-carbethoxyaminodiphenyl (IV; R = Me).—2-Nitro-4-carbethoxyaminodiphenyl (15 g.) was dissolved in alcohol (400 ml.), and reduced with hydrogen at 20 atmospheres' pressure in the presence of palladised charcoal (5 g.; 3%). The alcoholic solution of 2-amino-4-carbethoxyaminodiphenyl thus obtained was at first colourless, but assumed a deep purple colour on exposure. The amine was a colourless oil, which could not be induced to crystallise. On being warmed with acetic anhydride it was readily converted into the *acetyl* derivative (14 g.) which crystallised from alcohol in white needles, m. p. 169·5° (Found: C, 68·5; H, 6·1; N, 9·4. $C_{17}H_{18}O_3N_2$ requires C, 68·45; H, 6·1; N, 9·4%).

2-Carbethoxyamino-9-methylphenanthridine (V; R = Me).—When a solution of the foregoing acetyl compound (10 g.) in phosphoryl chloride (10 ml.) was heated, vigorous reaction took place and the product began to crystallise as a salt after a few minutes. After 30 minutes' refluxing, excess of phosphoryl chloride was cautiously decomposed with water, and alkali added to neutrality; the solid *product* crystallised from alcohol in white plates (7·5 g.), m. p. 197° (Found: C, 72·8; H, 5·9; N, 9·9. $C_{17}H_{16}O_2N_2$ requires C, 72·85; H, 5·75; N, 10·0%). When this substance was dissolved in hot 2N-hydrochloric acid, the *hydrochloride* crystallised in lemon-yellow needles, unmolten at 300° (Found for dried salt: N, 9·05; Cl, 11·1. $C_{17}H_{17}O_2N_2Cl$ requires N, 8·85; Cl, 11·2%).

2-Amino-9-methylphenanthridine.—The corresponding urethane (2 g.) was dissolved in sulphuric acid (2 ml.) and water (1 ml.), and the solution heated at 150° for 30 minutes. Dilution with water and neutralisation precipitated the *amine*, which crystallised from aqueous alcohol in cream-coloured plates, m. p. 174—175° (Found: C, 80·6; H, 5·6; N, 13·65. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·45%).

2-Amino-9: 10-dimethylphenanthridinium Bromide (VI).—2-Carbethoxyamino-9-methylphenanthridine (6 g.) was dissolved in nitrobenzene (60 ml.) at 160° and treated with methyl sulphate (3 ml.). The yellow crystals of the quaternary methosulphate, which separated immediately in quantitative yield, were washed with boiling benzene and dissolved in water. On addition of potassium bromide to the solution *2-carbethoxyamino-9: 10-dimethylphenanthridinium bromide* crystallised in small yellow needles, m. p. 247° (decomp.) (Found for dried salt: N, 7·65; Br, 21·7. $C_{18}H_{19}O_2N_2Br$ requires N, 7·45; Br, 21·35%). A solution of the methosulphate (5 g.) in concentrated sulphuric acid (7 ml.) and water (3·5 ml.) was heated at 150° for 15 minutes. Dilution with water and neutralisation with ammonia furnished a deep red solution from which, on addition of potassium bromide, the required *bromide* crystallised in small red needles, unmolten at 300° (Found: N, 9·1; Br, 26·2. $C_{15}H_{15}N_2Br$ requires

N, 9·25; Br, 26·4%). This salt was readily soluble in water, or in methyl alcohol, but less soluble in ethyl alcohol.

2-*Carbethoxyamino*-9-p-*nitrophenylphenanthridine* (V; R = *p*-C_6H_4·NO_2).—Oily 2-amino-4-carbethoxyaminodiphenyl (12·5 g.) was dissolved in nitrobenzene at 150° and treated with *p*-nitrobenzoyl chloride (10 g.). After 30 minutes, evolution of hydrogen chloride having ceased, the solution was cooled to allow 2-p-*nitrobenzamido*-4-*carbethoxyaminodiphenyl* (IV; R = *p*-C_6H_4·NO_2) to crystallise. Recrystallisation from glacial acetic acid furnished deep yellow prisms, m. p. 226·5° (Found: C, 64·7; H, 4·85; N, 10·3. $C_{22}H_{19}O_5N_3$ requires C, 65·2; H, 4·75; N, 10·35%). This substance (25 g.) was cyclised by refluxing it with phosphoryl chloride (25 ml.) for 45 minutes and then cautiously decomposing the excess of reagent with water. The solid product was dissolved in hot pyridine (100 ml.) and the solution treated with hot water (50 ml.). The *phenanthridine* (14 g.) crystallised in yellow needles, m. p. 258—259° (efferv.) (Found: C, 68·35; H, 4·65; N, 11·0. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·45; N, 10·85%). This compound was hydrolysed in the manner already described. On dilution of the sulphuric acid solution a purple sulphate, insoluble in water, separated; when it was stirred with ammonia it was converted into 2-*amino*-9-p-*nitrophenylphenanthridine*, which crystallised from pyridine in small brownish-red needles, m. p. 259° (Found: C, 72·25; H, 4·25; N, 13·65. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·15; N, 13·35%).

2-*Amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium Chloride* (as I; R = NO_2, R″ = NH_2, R′ = H).—Methyl sulphate (8·5 ml.) was added to a solution of 2-carbethoxyamino-9-*p*-nitrophenylphenanthridine (17 g.) in nitrobenzene (100 ml.) at 175°. The quaternary methosulphate began to crystallise at once, and after 10 minutes at 175°, it was collected and washed with hot benzene. The salt was dissolved in a large volume of boiling water, filtered from a small amount of unchanged starting material, and treated with hydrochloric acid. 2-*Carbethoxyamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride* (as I; R = NO_2, R″ = NH·CO_2Et, R′ = H) crystallised in yellow prismatic needles (15 g.), m. p. 252—254° (decomp.) (Found: C, 63·0; H, 4·6; N, 9·7; Cl, 8·05. $C_{23}H_{20}O_4N_3Cl$ requires C, 63·1; H, 4·6; N, 9·6; Cl, 8·1%). The methosulphate (6·5 g.) was hydrolysed by sulphuric acid (7 ml. of concentrated acid and 3·5 ml. of water) by being heated at 150° for 30 minutes. On dilution with water a deep red acid salt crystallised, which on neutralisation and addition of sodium chloride was converted into 2-*amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride*, which crystallised from water in almost black plates, m. p. 222—224° (decomp.) (Found: C, 62·4; H, 5·2; N, 10·85; Cl, 9·4; loss at 100°, 4·85. $C_{20}H_{16}O_2N_3Cl,H_2O$ requires C, 62·55; H, 4·75; N, 10·95; Cl, 9·25; H_2O, 4·7%). When a solution of the salt (3 g.) in hot glacial acetic acid (6 ml.) was treated with acetic anhydride (1·5 ml.) the *acetyl* derivative crystallised quantitatively. On recrystallisation from a large volume of water it formed deep yellow prisms (3·1 g.), unmolten at 300° (Found: N, 10·2; Cl, 8·45; loss at 100°, 2·2. $C_{22}H_{18}O_3N_3Cl,0·5H_2O$ requires N, 10·1; Cl, 8·5; H_2O, 2·1%).

2-*Acetamido*-9-p-*aminophenyl*-10-*methylphenanthridinium Chloride* (as I; R = NH_2, R″ = NH·COMe, R′ = H).—The foregoing acetamido-nitro-salt (2 g.) was added with stirring to a boiling suspension of "reduced" iron (4 g.) in water (100 ml.). Reduction took place rapidly, and after hot filtration the product crystallised in minute yellow needles. It was purified by warming with 0·2N-hydrochloric acid (50 ml.), thereby leaving undissolved a trace of unreduced nitro-compound. Neutralisation of the filtrate liberated the sparingly soluble *product*, and sufficient boiling water was added to bring this into solution. With cooling orange-yellow prisms of the desired salt separated (1·6 g.), m. p. 283° (decomp.) (from a bath pre-heated to 260°) (Found: N, 10·7; Cl, 9·05; loss at 100°, 5·15. $C_{22}H_{20}ON_3Cl,H_2O$ requires N, 10·6; Cl, 8·95; H_2O, 4·55%). A solution of this salt (4 g.) in hot 0·2N-hydrochloric acid (80 ml.) was stirred with ethyl chloroformate (2 ml.). 2-*Acetamido*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride* (as I; R = NH·CO_2Et, R″ = NH·COMe, R′ = H) slowly crystallised from the mixture. It crystallised from water in orange-yellow plates, m. p. 193—195° (decomp.) (Found: N 8·85; Cl, 7·4; loss at 100°, 7·0. $C_{25}H_{24}O_5N_3Cl,2H_2O$ requires N, 8·65; Cl, 7·3; H_2O, 7·4%).

2-*Amino*-9-p-*aminophenyl*-10-*methylphenanthridinium Bromide* (I; R = R″ = NH_2, R′ = H).—(*a*) A solution of 2-acetamido-9-*p*-aminophenyl-10-methylphenanthridinium chloride (1 g.) in 4N-hydrochloric acid (8 ml.) was refluxed for 30 minutes and then neutralised with ammonia. The *diamino-chloride* was liberated as a red oil, which soon solidified. It crystallised from a small volume of water in magnificent deep red prisms, m. p. 257° (decomp.) (Found for dried salt: N, 12·75; Cl, 10·35. $C_{20}H_{18}N_3Cl$ requires N, 12·55; Cl, 10·6%). The *bromide* crystallised from methyl alcohol in deep red needles, m. p. 254° (decomp.) (Found: C, 63·0; H, 4·5; N, 11·05; Br, 21·3. $C_{20}H_{18}N_3Br$ requires C, 63·15; H, 4·75; N, 11·05; Br, 21·05%).

(*b*) Reduction of 2-amino-9-*p*-nitrophenyl-10-methylphenanthridinium chloride (4·3 g.) with "reduced" iron gave an ill-defined red solid, which was dissolved in 5N-hydrochloric acid. A brown salt crystallised, which on addition to boiling water was converted into a micro-crystalline purple-red substance (1 g.) of which the nature has not yet been elucidated. Neutralisation of the acid filtrate furnished the desired salt, which was best purified by crystallisation of the bromide (2·0 g.) from methyl alcohol.

2-*Amino*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium Bromide* (I; R = NH·CO_2Et, R″ = NH_2, R′ = H).—2-Acetamido-9-*p*-carbethoxyaminophenyl-10-methylphenanthridinium chloride (2 g.) was refluxed with 2N-hydrochloric acid (20 ml.). The salt slowly dissolved, and after 1 hour the solution was cooled and neutralised with ammonia. The red oil thus liberated slowly changed to a mass of orange needles, which were best purified by conversion into the *bromide*, which crystallised from water in orange-red plates, m. p. 254—256° (decomp.) (Found: C, 61·35; H, 4·85; N, 9·55; Br, 18·1. $C_{23}H_{22}O_2N_3Br$ requires C, 61·05; H, 4·9; N, 9·3; Br, 17·7%).

By the same method the corresponding 7-acetamido-salt was converted into 7-*amino*-9-p-*carbethoxyaminophenyl*-10-*methylphenanthridinium chloride*, which crystallised from water in orange-red plates, m. p. 195° (decomp.) (Found: N, 9·65; Cl, 7·95; loss at 100°, 6·6. $C_{23}H_{22}O_2N_3Cl,1·5H_2O$ requires N, 9·65; Cl, 8·15; H_2O, 6·25%).

2-*Nitro*-3′-*aminodiphenyl*.—3-Nitrodiphenyl (25 g.) was nitrated as recommended by Case (*loc. cit.*), but the product was worked up by the method of Blakey and Scarborough (*J.*, 1927, 3000). The methyl alcohol mother-liquor from which the 3 : 4′-dinitrodiphenyl had been separated according to their method was concentrated to small bulk. The crude mixture (12 g.), consisting mainly of 2 : 3′-dinitrodiphenyl, which separated, was reduced with sodium polysulphide as previously described (Walls, *loc. cit.*) for a similar mixture of 2 : 4′- and 4 : 4′-dinitrodiphenyls. The crude semi-solid product was dissolved in 2N-hydrochloric acid, and by fractional crystallisation pure 2-nitro-3′-aminodiphenyl hydrochloride was obtained. By dissolution of this salt in water and neutralisation the base was liberated as an oil which set to a yellow crystalline solid (6 g.). Recrystallisation from methyl alcohol furnished yellow prisms, m. p. 83° (Found: C, 66·95; H, 4·9. Calc. for $C_{12}H_{10}O_2N_2$: C, 67·25; H, 4·7%).

2-*Amino*-3′-*carbethoxyaminodiphenyl* (VII).—A solution of the foregoing amine (37 g.) in boiling alcohol (200 ml.) was treated successively with diethylaniline (28 ml.) and dropwise with ethyl chloroformate (14 ml.). After 30 minutes' refluxing the solution was poured into excess of dilute hydrochloric acid, and the yellow oil thus liberated was extracted with ether. The extract was washed with dilute hydrochloric acid and then with water and dried (Na_2SO_4). Removal of ether left a quantitative yield of 2-nitro-3′-carbethoxyaminodiphenyl, which could not be induced to crystallise. It was reduced at room temperature in alcoholic solution (400 ml.) by hydrogen at 25 atmospheres, with palladised charcoal (15 g.; 3%) as catalyst. On evaporation of alcohol the *base* was obtained as a somewhat discoloured crystalline mass, which on recrystallisation from light petroleum (b. p. 60—80°) gave soft white plates, m. p. 88° (Found: C, 70·35; H, 6·7; N, 10·95. $C_{15}H_{16}O_2N_2$ requires C, 70·3; H, 6·3; N, 10·95%). On the base being warmed with acetic anhydride, the *acetyl* derivative crystallised. It crystallised from methyl alcohol in small white needles, m. p. 161° (Found: C, 68·35; H, 6·4; N, 9·45. $C_{17}H_{18}O_3N_2$ requires C, 68·45; H, 6·1; N, 9·4%).

6- *and* 8-*Carbethoxyamino*-9-*methylphenanthridines* (VIII).—When 2-acetamido-3′-carbethoxyaminodiphenyl (27 g.) and phosphoryl chloride (27 ml.) were heated together a vigorous reaction occurred with evolution of hydrogen chloride and immediate separation of white crystals. After 30 minutes' refluxing the mixture was decomposed with water and made alkaline. The white solid thus obtained was completely soluble in dilute sulphuric acid, thus indicating that ring-closure was quantitative. The isomerides were best separated by crystallisation of the sulphates. A solution of the mixture in alcohol (400 ml.) was treated with concentrated sulphuric acid (6 ml.), which precipitated 6-*carbethoxyamino*-9-*methylphenanthridine sulphate* as a mass of almost white needles (21 g.), which were recrystallised from alcohol (2·5 l.), m. p. 216° (decomp.) (Found: N, 7·35; S, 8·1. $C_{17}H_{16}O_2N_2,H_2SO_4$ requires N, 7·4; S, 8·45%). On evaporation of the mother-liquor 8-*carbethoxyamino*-9-*methylphenanthridine sulphate* crystallised in transparent yellow prisms (3 g.), m. p. 187° (decomp.) (Found: N, 7·55; S, 8·4%). 6-*Carbethoxyamino*-9-*methylphenanthridine* was liberated from its salt; it crystallised from benzene in colourless plates containing water of crystallisation evidently taken up from the damp solvent; it sintered at 110° and then had m. p. 163° (Found: C, 68·6; H, 5·8; N, 9·25; loss at 100°, 6·4. $C_{17}H_{16}O_2N_2,H_2O$ requires C, 68·45; H, 6·1; N, 9·4; H_2O, 6·05%). 8-*Carbethoxyamino*-9-*methylphenanthridine* crystallised from aqueous alcohol in colourless acicular prisms, m. p. 159·5° (Found: C, 68·9; H, 5·9; N, 9·4. $C_{17}H_{16}O_2N_2,H_2O$ requires C, 68·45; H, 6·05; N, 9·4%).

Hydrolysis of these urethanes with sulphuric acid (2 : 1) at 150° furnished: (a) 6-*Amino*-9-*methylphenanthridine*, which crystallised from aqueous alcohol in white prismatic needles, m. p. 196·5° (Found: C, 80·85; H, 5·8; N, 13·7. $C_{14}H_{12}N_2$ requires C, 80·7; H, 5·8; N, 13·45%); the *hydrochloride* crystallised from water in pale yellow needles, unmolten at 300° (Found for dried salt: N, 11·65; Cl, 14·55. $C_{14}H_{13}N_2Cl$ requires N, 11·45; Cl, 14·5%). (b) 8-*Amino*-9-*methylphenanthridine*, which crystallised from aqueous alcohol in cream-coloured prisms; it sintered at 70°, but after vacuum drying had m. p. 134·5° (Found: C, 81·05; H, 5·65; N, 13·6%); the *hydrochloride* crystallised from water in orange needles, unmolten at 300° (Found: N, 11·25; Cl, 14·6%).

8-*Hydroxy*-9-*methylphenanthridine* (IX; R = Me).—8-Amino-9-methylphenanthridine (0·5 g.) was diazotised in 2N-sulphuric acid solution (5 ml.) with sodium nitrite (0·2 g.). The solution was heated (steam-bath) until effervescence ceased, and the tarry product was extracted with sodium hydroxide solution. By neutralisation of the extract the hydroxyl compound was liberated as a yellow flocculent precipitate which was collected, dissolved in alcohol, and treated with a few drops of concentrated hydrochloric acid. The *hydrochloride* crystallised in small yellow needles, which on recrystallisation from alcohol formed large transparent greenish-yellow prisms, unmolten at 300° (Found: Cl, 14·2. $C_{14}H_{12}ONCl$ requires Cl, 14·4%).

6-*Amino*-9 : 10-*dimethylphenanthridinium Bromide*.—6-Carbethoxyamino-9-methylphenanthridine was converted quantitatively into the quaternary *methosulphate* by the method described for the 2-isomeride. The salt was readily soluble in water but was best recrystallised from alcohol, forming white needles, m. p. 238—242° (decomp.) (Found: C, 55·6; H, 5·7; N, 7·15; S, 7·95. $C_{19}H_{22}O_6N_2S$ requires C, 56·1; H, 5·45; N, 6·9; S, 7·9%). By hydrolysis with sulphuric acid the *bromide* was isolated, which crystallised from water in pale yellow prismatic needles, m. p. 297—299° (Found for dried salt: N, 9·2; Br, 26·25. $C_{15}H_{11}N_2Br$ requires N, 9·25; Br, 26·35%).

6- *and* 8-*Carbethoxyamino*-9-p-*nitrophenylphenanthridines* (X; R = NH·CO_2Et).—A solution of 2-amino-3′-carbethoxyaminodiphenyl (20 g.) in boiling chlorobenzene (200 ml.) was treated with *p*-nitrobenzoyl chloride (14 g.). After 30 minutes' boiling evolution of hydrogen chloride had ceased, and, with cooling, 3-*carbethoxyamino*-2′-*p*-*nitrobenzamidodiphenyl* (30 g.) crystallised from the mixture; it crystallised from alcohol in cream-coloured needles (27 g.), which partially melted at 161—162°, resolidified, and melted sharply at 176° (Found: C, 65·35; H, 4·85; N, 10·4. $C_{22}H_{19}O_5N_3$ requires C, 65·2; H, 4·75; N, 10·35%). This substance (20 g.) and phosphoryl chloride (30 ml.) were heated in a bath at 130° for 1 hour, and then cautiously decomposed with water. The solid product was heated with aqueous alkali, washed, and dried; it was then refluxed with alcohol (800 ml.) and filtered hot from the 6-*isomeride* (6·2 g.). This product crystallised from a large volume of acetone in hard colourless

prisms, m. p. 248—250° (decomp.); from pyridine, in which it was fairly soluble, it gave clumps of small needles (Found: C, 68·25; H, 4·35; N, 11·05. $C_{22}H_{17}O_4N_3$ requires C, 68·2; H, 4·45; N, 10·85%). By fractional crystallisation of the alcoholic mother-liquor a further quantity of the 6-isomeride (1 g.) and the 8-*isomeride* (9·5 g.) were obtained. The latter crystallised from alcohol, in which it was much more soluble than its isomeride, in pale yellow prisms, m. p. 194° (Found: C, 68·4; H, 4·35; N, 10·9%). Hydrolysis of the 6-isomeride with sulphuric acid furnished 6-*amino*-9-p-*nitrophenylphenanthridine* (X; R = NH_2), which was very sparingly soluble in alcohol, but crystallised from pyridine in yellow needles, m. p. 260° (Found: C, 72·7; H, 4·3; N, 13·35. $C_{19}H_{13}O_2N_3$ requires C, 72·4; H, 4·15; N, 13·35%). This substance possessed weak basic properties, forming an insoluble yellow sulphate. 8-*Amino*-9-p-*nitrophenylphenanthridine*, similarly prepared, crystallised from alcohol in golden yellow needles, m. p. 180° (Found: C, 72·55; H, 4·35; N, 13·8%). It formed a bright red, slightly soluble sulphate.

Whereas the 6-amine could readily be reconverted quantitatively in acetone solution into the urethane by the general method, with the 8-amine a very poor yield was obtained, a result attributed to steric hindrance.

8-*Hydroxy*-9-p-*nitrophenylphenanthridine* (IX; R = *p*-$C_6H_4{\cdot}NO_2$).—A solution of the 8-amine (0·5 g.) in concentrated sulphuric acid (5 ml.) was cooled in ice and diazotised with a solution of sodium nitrite (0·11 g.) in concentrated sulphuric acid (2 ml.). The mixture was diluted with ice, and the yellow solution thus obtained heated (steam-bath) until effervescence ceased. The brownish-yellow precipitated *product* was insoluble in alkali. It crystallised from nitrobenzene in buff needles, m. p. 262—263° (Found: N, 9·05. $C_{19}H_{12}O_3N_2$ requires N, 8·9%).

6-*Hydroxy*-9-p-*nitrophenylphenanthridine* was similarly obtained in high yield. It was readily purified by solution in aqueous alkali and reprecipitation by acetic acid, and crystallised from cellosolve in buff prisms, m. p. 280—282° (Found: N, 9·0%).

6-*Amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium Chloride* (II; R = NO_2, R′ = NH_2).—6-Carbethoxyamino-9-*p*-nitrophenylphenanthridine was converted into its quaternary salt by the method described for the 2-isomeride. The methosulphate was precipitated from the nitrobenzene reaction mixture by benzene as a semi-solid mass, which was washed with hot benzene, dried, and dissolved in water. Both the methosulphate and the *chloride* were liable to form viscid gels with water, but the latter crystallised from alcohol in cream-coloured needles, m. p. 221—223° (decomp.) (Found: C, 60·65; H, 4·95; N, 9·25; Cl, 8·1; loss at 100°, 4·05. $C_{22}H_{20}O_4N_3Cl,H_2O$ requires C, 60·65; H, 4·85; N, 9·25; Cl, 7·8; H_2O, 3·95%). Hydrolysis with sulphuric acid, followed by dilution, and neutralisation with ammonia furnished the *amino-nitro*-salt, which crystallised from water in brownish-yellow plates, m. p. 217° (decomp.) (Found for dried salt: N, 11·4; Cl, 9·45. $C_{20}H_{16}O_2N_3Cl$ requires N, 11·5; Cl, 9·7%).

6-*Amino*-9-p-*aminophenyl*-10-*methylphenanthridinium Chloride* (II; R = R′ = NH_2).—The foregoing salt (3 g.) was refluxed with alcohol (60 ml.) and concentrated hydrochloric acid (6 ml.) until a clear solution was obtained. Addition of stannous chloride (6·5 g.) precipitated a yellow salt, but as refluxing continued this went into solution as light-brown prismatic crystals began to separate. This sparingly soluble salt (3 g.) was dissolved in hot water (600 ml.), the solution neutralised, and filtered from stannic hydroxide. With cooling the *diamino*-salt crystallised in light brown prisms, unmolten at 300° (Found: C, 71·4; H, 5·1; N, 12·55; Cl, 10·7. $C_{20}H_{18}N_3Cl$ requires C, 71·5; H, 5·35; N, 12·5; Cl, 10·6%). The same compound was obtained by reduction with iron and water.

The corresponding salts of the 8-series, which were much more soluble in water, were prepared by similar methods.

8-*Carbethoxyamino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride*, obtained in poor yield, crystallised from water in transparent orange prisms, m. p. 180—185° (decomp.), dependent on rate of heating (Found: C, 57·6; H, 4·85; N, 9·05; Cl, 7·65; loss at 100°, 7·6. $C_{22}H_{20}O_4N_3Cl,2H_2O$ requires C, 58·3; H, 5·1; N, 8·85; Cl, 7·5; H_2O, 7·6%).

8-*Amino*-9-p-*nitrophenyl*-10-*methylphenanthridinium chloride* crystallised from water in black prisms (ruby-red by transmitted light), m. p. 232—234° (decomp.) (Found: N, 10·7; Cl, 9·15; loss at 100°, 4·25. $C_{20}H_{16}O_2N_3Cl,H_2O$ requires N, 10·95; Cl, 9·25; H_2O, 4·7%).

8-*Amino*-9-p-*aminophenyl*-10-*methylphenanthridinium bromide* crystallised from water in light red prisms, m. p. 245—246° (decomp.) (Found: N, 11·0; Br, 21·2. $C_{20}H_{18}N_3Br$ requires N, 11·05; Br, 21·05%).

4-*Carbethoxyamino*-2′-p-*nitrophenylacetamidodiphenyl*.—A solution of 4-carbethoxyamino-2′-acetamidodiphenyl (20 g.; Walls, *loc. cit.*) was refluxed in alcohol (140 ml.) and concentrated sulphuric acid for 2½ hours. 2N-Ammonia was added to neutrality, and 2-amino-4′-carbethoxyaminodiphenyl crystallised in almost quantitative yield; on recrystallisation from light petroleum (b. p. 60—80°) white prismatic needles were obtained, m. p. 96°, alone or in admixture with an authentic specimen. *p*-Nitrophenylacetyl chloride (18 g.) was added portionwise to a solution of this amine (21 g.) in hot chlorobenzene (180 ml.), and the mixture was refluxed for 20 minutes, hydrogen chloride being evolved. After cooling, the crystalline *product* (33 g.) was collected, washed with light petroleum (b. p. 80—100°) followed by light petroleum (b. p. 40—60°), and dried. On crystallisation from alcohol or aqueous dioxan it formed small colourless feathery needles, m. p. 209—210° (Found: C, 66·05; H, 5·05; N, 10·2. $C_{23}H_{21}O_5N_3$ requires C, 65·9; H, 5·05; N, 10·0%).

7-*Carbethoxyamino*-9-p-*nitrobenzylphenanthridine* (XII).—The foregoing amide (20 g.) was refluxed with phosphoryl chloride (60 ml.) for 1 hour. The mixture was poured into water, and the precipitated bright yellow salt dissolved in hot aqueous pyridine, from which the *phenanthridine* derivative crystallised in almost quantitative yield. It crystallised from benzene in fine colourless needles, m. p. 186—187° (Found: C, 68·75; H, 4·85; N, 10·35. $C_{22}H_{19}O_4N_3$ requires C, 68·85; H, 4·75; N, 10·45%).

7-*Amino*-9-p-*nitrobenzylphenanthridine*.—The 7-carbethoxyamino-compound (5 g.) was heated with sulphuric acid (2 : 1) at 150° for 45 minutes, diluted with water, and the sparingly soluble sulphate collected and crystallised from aqueous pyridine. The *amine* was thus obtained in 90% yield, crystallising

from dioxan in deep yellow needles, m. p. 244—247° (decomp.) (Found: C, 72·7; H, 4·8; N, 12·5. $C_{20}H_{15}O_2N_3$ requires C, 72·95; H, 4·6; N, 12·75%). Acetylation with acetic anhydride furnished the *acetyl* derivative, which crystallised from dioxan in pale yellow needles, m. p. 252—254° (decomp.) (Found: C, 71·05; H, 5·0; N, 11·25. $C_{22}H_{17}O_3N_3$ requires C, 71·15; H, 4·6; N, 11·3%).

7-*Carbethoxyamino*-9-p-*nitrobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = NO_2, R′ = $NH{\cdot}CO_2Et$).—7-Carbethoxyamino-9-*p*-nitrobenzylphenanthridine (5 g.) in nitrobenzene (35 ml.) at 180° was treated with methyl sulphate (3 ml.). With cooling a precipitate formed, consisting of a mixture of starting material and *methosulphate*, which on crystallisation from alcohol yielded the latter (50% yield) in pale yellow needles, m. p. 234—236° (decomp.) (Found: C, 57·05; H, 5·05; N, 7·9. $C_{25}H_{25}O_9N_3S$ requires C, 56·9; H, 4·8; N, 7·95%). The *chloride* crystallised from dilute hydrochloric acid in deep yellow needles, m. p. 221° (decomp.) (Found: N, 9·65; Cl, 7·9. $C_{24}H_{22}O_4N_3Cl$ requires N, 9·3; Cl, 7·85%). When either salt was boiled with water, part dissolved and part was converted into a less soluble red substance. The salts crystallised normally from dilute acid.

7-*Amino*-9-p-*nitrobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = NO_2, R′ = NH_2).—Hydrolysis of the foregoing salt (6 g.) with sulphuric acid followed by dilution with water gave a red precipitate, which was collected and dissolved in boiling water. After addition of barium chloride (1 g.) and separation of barium sulphate, the solution deposited red platelets, m. p. 185° (decomp.), of the desired *salt*. On being dried at 110°/0·05 mm. the salt lost water of crystallisation and became almost black, regaining water and reverting to its original red colour on exposure to air (Found for dried salt: N, 10·95; Cl, 9·15. $C_{21}H_{16}O_2N_3Cl$ requires N, 11·05; Cl, 9·35%). A solution of this salt in glacial acetic acid was readily converted into 7-*acetamido*-9-p-*nitrobenzyl*-10-*methylphenanthridinium chloride* by acetic anhydride; yellow prismatic needles, m. p. 245° (decomp.), were obtained from alcohol (Found: N, 9·9; Cl, 8·35. $C_{23}H_{20}O_3N_3Cl$ requires N, 9·95; Cl, 8·4%). The same salt was also prepared from 7-acetamido-9-*p*-nitrobenzylphenanthridine and methyl sulphate. It reacted with water in a manner similar to the corresponding 7-carbethoxyamino-salt.

7-*Amino*-9-p-*aminobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = R′ = NH_2).—When the amino-nitro-salt was reduced by iron and water, the *product* separated from the hot filtrate as a gel, which could, however, be filtered off and dried; it crystallised from water in a voluminous mass of microscopic orange needles, m. p. *ca.* 205° (decomp.) (Found: C, 71·45; H, 5·8; N, 12·25; Cl, 10·3. $C_{21}H_{20}N_3Cl$ requires C, 72·05; H, 5·75; N, 12·0; Cl, 10·15%).

7-*Carbethoxyamino*-9-p-*aminobenzyl*-10-*methylphenanthridinium chloride* (XIII; R = NH_2, R′ = $NH{\cdot}CO_2Et$) was obtained by iron–water reduction of the corresponding nitro-salt. It crystallised from water in fine orange needles, m. p. 206—210° (decomp.) (bath preheated to 200°) (Found: N, 10·0; Cl, 8·25. $C_{24}H_{24}O_2N_3Cl$ requires N, 9·95; Cl, 8·4%). On hydrolysis with sulphuric acid this compound yielded the diamino-salt described above. When an aqueous solution of either salt was stirred with ethyl chloroformate, 7-*carbethoxyamino*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium chloride* crystallised in bright yellow micro-needles, m. p. *ca.* 220° (decomp.) (Found: N, 8·55; Cl, 7·1. $C_{27}H_{26}O_4N_3Cl$ requires N, 8·5; Cl, 7·2%).

7-*Acetamido*-9-p-*aminobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = NH_2, R′ = $NH{\cdot}COMe$).—The acetamido-nitro-salt was reduced with iron–water; the *amino*-salt crystallised from water in deep yellow micro-needles, m. p. 262° (decomp.) (bath preheated to 250°) (Found: N, 10·7; Cl, 8·45. $C_{23}H_{22}ON_3Cl$ requires N, 10·7; Cl, 9·05%). The sparingly soluble *bromide* formed orange micro-crystals, m. p. 274° (decomp.) (Found: N, 9·6; Br, 18·35. $C_{23}H_{22}ON_3Br$ requires N, 9·65; Br, 18·35%). Treatment of an aqueous solution of the chloride with ethyl chloroformate yielded 7-*acetamido*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium chloride*, which crystallised from water in pale yellow micro-needles, m. p. 242° (decomp.) (Found: N, 9·45; Cl, 7·15. $C_{26}H_{24}O_3N_3Cl$ requires N, 9·05; Cl, 7·65%). The *bromide* crystallised from water in yellow micro-needles, m. p. 255° (decomp.) (Found: N, 8·7; Br, 15·7. $C_{26}H_{24}O_3N_3Br$ requires N, 8·25; Br, 15·75%).

7-*Amino*-9-p-*carbethoxyaminobenzyl*-10-*methylphenanthridinium Chloride* (XIII; R = $NH{\cdot}CO_2Et$, R′ = NH_2).—The acetamido-carbethoxyamino-salt (6·5 g.) was refluxed for 1½ hours with 2N-hydrochloric acid (60 ml.) during which period the solid slowly dissolved. The hot solution was neutralised with 2N-ammonia to liberate a red gum, which slowly set to a red solid, m. p. 55—80°. This hydrated *salt* was heated with *n*-propyl alcohol (50 ml.), and converted into an orange powder, m. p. 244° (decomp.), which was crystallised by dissolving it in anhydrous methanol and adding dry ether (Found: N, 9·9; Cl, 8·35. $C_{24}H_{24}O_2N_3Cl$ requires N, 9·95; Cl, 8·4%).

9-p-*Nitrobenzylphenanthridine*.—Condensation of *o*-xenylamine (5·5 g.) and *p*-nitrophenylacetyl chloride (6·5 g.) in boiling chlorobenzene (35 ml.) afforded 2-p-*nitrophenylacetamidodiphenyl*, which crystallised from alcohol in long colourless needles, m. p. 188—189° (Found: C, 72·6; H, 4·9; N, 8·4. $C_{20}H_{16}O_3N_2$ requires C, 72·3; H, 4·85; N, 8·45%). This product (3 g.) was readily converted by phosphoryl chloride into the *phenanthridine* (1·9 g.), which crystallised from benzene or alcohol in clumps of colourless needles, m. p. 168—169° (Found: C, 76·4; H, 4·6; N, 9·0. $C_{20}H_{14}O_2N_2$ requires C, 76·4; H, 4·5; N, 8·9%).

9-p-*Nitrobenzyl*-10-*methylphenanthridinium methosulphate* was obtained from the foregoing compound (5 g.) and methyl sulphate (5 ml.) in nitrobenzene (30 ml.) at 180°. The crystalline product formed straw-coloured prismatic needles from methanol, m. p. 238° (decomp.) (Found: N, 6·5; S, 7·4. $C_{22}H_{20}O_6N_2S$ requires N, 6·35; S, 7·3%). This salt was only partially soluble in water, a red suspension, soluble in dilute acid, being obtained.

9-p-*Aminobenzyl*-10-*methylphenanthridinium chloride* was the product of iron–water reduction of the preceding nitro-salt. It crystallised from water in deep orange felted needles of a hydrate (2·5 H_2O), m. p. *ca.* 115—120° (efferv. at 130°), unchanged by dehydration at 80°/0·05 mm. (Found: N, 8·45; Cl, 9·45. $C_{21}H_{19}N_2Cl$ requires N, 8·35; Cl, 10·6%). The *bromide*, orange needles, m. p. 215—218°, gave satisfactory analytical results (Found: N, 7·35; Br, 21·15. $C_{21}H_{19}N_2Br$ requires N, 7·4; Br, 21·1%). The *carbethoxyl* compound crystallised as a hydrate in cream-coloured needles, m. p. 60°, efferv. 110°, resolidifying and melting finally at *ca.* 205° (decomp.). After drying at 110°/15 mm., the

compound crystallised from *n*-propyl alcohol in pale yellow micro-crystals, m. p. 220° (decomp.) (Found: N, 6·85; Cl, 8·7. $C_{24}H_{23}O_2N_2Cl$ requires N, 6·9; Cl, 8·75%).

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48. *Alginic Acid Acetate.*

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Alginic acid and sodium and calcium alginate react at room temperature with keten to produce derivatives in which approximately one acetyl grouping is contained in each repeating unit of the chain polymers. Some properties of these acetylated materials are described.

ALGINIC acid reacts at room temperature with keten to form a colourless ester acid (I), practically insoluble in water, acetone, ethyl alcohol, methyl alcohol, ether, acetic acid, glycerol, ethyl acetoacetate, or chloroform, which can be converted into the sodium salt (II) or the calcium salt (III) by treating it with equivalent quantities of sodium or calcium hydroxide solution; these salts could also be prepared by direct reaction of keten with sodium and calcium alginate. If dried (I) is treated with sodium hydroxide, (II) is obtained in the form of a non-transparent gel, which binds about 800 mols. of water/g.-equivalent and is insoluble in acetone, ethyl alcohol, ether, acetic acid, ethyl acetoacetate, aniline, or aqueous solutions of various salts, *e.g.*, ammonium sulphate or potassium palmitate. Gels of similar properties can be prepared by bringing (I) in contact with solutions of potassium hydroxide, ammonia, trimethylamine, or guanidinium carbonate. If (I) is converted into (II) at about 60°, the salt is obtained as a transparent jelly which contains about 2500 mols. of water/g.-equivalent; this jelly can also be made by dispersing the moderately swollen form of (II) in glycerol or triethanolamine and adding water to the dispersion. A rapid de-swelling of the jelly is brought about by conversion into (I) or (III). If the glycerol dispersion of (II) is mixed with 0·1M-solutions containing calcium, magnesium, copper, or ferric ions, water-insoluble precipitates are formed.

The analyses of (I), (II), and (III) show that approximately one acetyl grouping has been introduced into each repeating unit of the chain polymers, but it is not claimed that acetyl derivatives of definite composition have been prepared. No attempt has been made to use the keten method under different conditions, *e.g.*, with catalysts, in order to obtain products of a higher acetyl content.*

The rate of alkaline hydrolysis of (II) is so great at room temperature that the direct titration of the carboxyl grouping in (I) had to be done by a special technique described below; at room temperature, on the other hand, acid hydrolysis is slow.

In order to find out whether the acetylation with keten gives rise to a marked degradation, viscosity determinations were made with solutions containing sodium alginate prepared by hydrolysis of the acetyl derivatives, taking into account the experiments of Rose (Ph. D. Thesis, London, 1937) and of Heen (*Kolloid-Z.*, **1938**, **83**, 304); these tests lead to the following conclusions. During the acetylation of calcium alginate no detectable breakdown of the chain polymer appears to occur, but during the reaction with sodium alginate and with free alginic acid some degradation takes place; the viscosity of solutions containing the "recovered" sodium alginate is in all cases far higher, however, than that of solutions of low molecular uronic acids.

EXPERIMENTAL.

A 1% aqueous solution of commercial sodium alginate (η, 40 centistokes at 25°) was percolated through beds of Amberlite and Zeo-carb, and mixed with excess of N-hydrochloric acid or 0·5M-calcium acetate. The alginic acid (IV) or the calcium alginate (V) thus obtained was strained off, thoroughly washed with water, and treated with acetone until at least 95% of the gel water had been replaced. The fully acetone-swollen (IV) was suspended in acetone and mixed with an equivalent amount of N-sodium hydroxide; the sodium alginate (VI) was strained off and suspended for 24 hours in a fresh portion of dry acetone. 60 G. of fully acetone-swollen (IV) were suspended in 200 c.c. of acetone, and

* Such products have been prepared by other methods; compare Gomez, *Inst. Espan. Oceanograph., Notas y Resumenes*, Ser. II, 1933, **74**, 98; Barry, Dillon, and O'Muineachain, *Sci. Proc. Roy. Dublin Soc.*, 1933—38, **21**, 289; Cunningham, Chamberlain, and Speakman, *Nature*, 1946, **158**, 553; Carson and Maclay, *J. Amer. Chem. Soc.*, 1946, **68**, 1015.

keten was passed for 7 hours through the suspension (20°) at 0·06 g.-mol./hour. (I) was strained off, washed with acetone, water, ethyl alcohol, and ether (II and III were similarly washed), and dried at room temperature. A known quantity of (I) was suspended in water containing some phenolphthalein, and, while nitrogen was passed through the rapidly stirred mixture, successive portions of 0·3 c.c. of 0·1N-sodium hydroxide were added; after the addition of each portion the time (t) for disappearance of the pink colouration of the indicator was noted. In the first stage it was 1—2 minutes, but after a certain amount of alkali had been added it rose abruptly to 10—15 minutes (second stage). It is assumed that during the first stage a diffusion step and during the second stage the alkaline hydrolysis determines the value of t; and the alkali added during the first stage was assumed to have reacted with the free carboxyl groups. Acetyl determinations of (I), (II), or (III) were made by adding excess of 0·1N-sodium hydroxide; after 24 hours the excess was back-titrated, control determinations having shown that hydrolysis was complete [Found: C, 43·5; H, 5·2; N, < 0·2; S< 0·2; P< 0·2; carboxyl (titration), 18 ± 1; carboxyl (Tollens–Le Fèvre method), 19·4 ± 0·6; acetyl, 19 ± 1; acetyl + carboxyl, 36·8 ± 0·4; ash, 0·5. $(C_8H_{10}O_8)_x$ requires C, 41·0; H, 4·3%; carboxyl, 18·8; acetyl, 18·4; carboxyl + acetyl, 37·2%].

In estimating the approximate rate of the acid hydrolysis of (I), three portions, each containing 0·00194 g.-equiv., were placed in 10·0 c.c. of 0·1N-hydrochloric acid, the time and temperature being as follows: (1) 20 hours, 20°; (2) 93 hours, 20°; (3) 66 hours, 58°. In each run the insoluble residue obtained was filtered off and slowly washed with 1 l. of water; titration of the combined filtrate and washing showed that the hydrolysis was respectively 7·9, 20, and 100%.

0·5 G. of dried (I) was placed in water and 19 c.c. of 0·1N-sodium hydroxide were added while stirring, the gel (II*a*) being filtered off after 2 hours. Fully acetone-swollen (VI) was treated with keten under conditions similar to those specified above, giving (II*b*). Both samples were dried first at 20° and then at 100° to constant weight, (III) being dried in the same way [Found: (II*a*): C, 35·6; H, 4·0; Na, 8·4; acetyl, 17·9. (II*b*): C, 37·3; H, 3·9; Na, 8·2; acetyl, 15·0. $(C_8H_9O_8Na)_x$ requires C, 37·5; H, 3·5; Na, 9·0; acetyl, 16·8%].

0·5 G. of dried (I) and 47 c.c. of 0·04N-calcium hydroxide were mixed under conditions similar to those prevailing during the preparation of (II), giving (III*a*). Fully acetone-swollen (V), containing 0·029 g.-equiv., was placed in 350 c.c. of acetone, and keten was passed for 22 hours through the suspension (25°), at 0·02 g.-mol./hour, giving (III*b*) {Found, (III*a*) C, 37·2; H, 4·0; Ca, 7·5; acetyl, 15·4. (III*b*) C, 38·5; H, 4·5; Ca, 7·9; acetyl, 13·2. $[(C_8H_9O_8)_2Ca]_x$ requires C, 37·9; H, 3·6; Ca, 7·9; acetyl, 17·0%}. Results of typical viscosity measurements are in the accompanying Table. (I), (II), and (III) used for these tests were washed as described above but not dried.

	Normality of soln. with respect to			η (centistokes, 25°) of soln. containing	
Alginates.	Na alginate.	Na acetate.	NaCl.	"Recovered" Na alginate.	Na alginate of control test.
(I)	0·040	0·040	0·007	4	18
(II*b*)	0·028	0·028	0·23	6	9
(III*b*)	0·030	0·030	0·20	14	13·8

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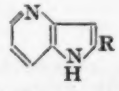
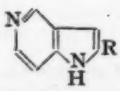
49. *The Synthesis of Derivatives of 4- and 5-Azaindole.*

By G. R. CLEMO and G. A. SWAN.

4-Azaindole (I, R = H), *2-methyl-4-azaindole* (I, R = Me) and *2-methyl-5-azaindole* (II, R = Me) have been synthesised.

THE preparation of derivatives of 6- and 7-azaindole by cyclisation of the appropriate acylamidopicolines has been described by Koenigs and Fulde (*Ber.*, 1927, **60**, 2106) and Clemo and Swan (*J.*, 1945, 603), respectively. The present communication records the synthesis of *4-azaindole* (I, R = H), *2-methyl-4-azaindole* (I, R = Me), and *2-methyl-5-azaindole* (II, R = Me) by the same general method.

(I.)  (II.) 

For the preparation of the last, the hitherto unknown *4-amino-3-picoline* was required. Koenigs and Greiner (*Ber.*, 1931, **64**, 1049) prepared 4-aminopyridine by the action of ammonia on 4-pyridylpyridinium dichloride (obtained by the action of thionyl chloride on pyridine). Application of this method to β-picoline gave a product which appears to be the required 4-amino-3-picoline, for it gave an azaindole derivative, from which it follows that the amino-group must be in a position *o*- to the methyl group, *i.e.*, in position 2 or 4; further, since the product differed from 2-amino-3-picoline (Seide, *Ber.*, 1924, **57**, 1802), it must be 4-amino-3-picoline. The intermediate pyridinium salt was not isolated, and the yield of the amino-picoline was low, the

reaction also leading to the formation of a sulphur-containing *product*, the structure of which has not been definitely ascertained: it may be a dipicolyl sulphide (cf. Crum and Robinson, *J.*, 1943, 561), although attempts to oxidise this to the corresponding sulphone failed. Treatment of the intermediate pyridinium salt with water yielded 4-*hydroxy*-3-*picoline*, which was also obtained by the action of nitrous acid on 4-amino-3-picoline. By the action of ammonia, the hydroxy- could be converted into the amino-compound.

By cyclisation of 4-*acetamido*-3-*picoline* with sodium ethoxide, 2-methyl-5-azaindole was obtained in *ca.* 1% yield, but cyclisation of the corresponding 4-*formamido*-compound to give 5-azaindole itself was not successful, even when potassium ethoxide was used as condensing agent. The action of acetic anhydride on 3-amino-2-picoline gave a product which appeared to be a *diacetyl* derivative; and this was cyclised to give 2-methyl-4-azaindole in good yield. The cyclisation of the corresponding *formyl* derivative was not achieved by the use of sodium ethoxide, although with potassium ethoxide the required 4-azaindole was obtained in a 20% yield. Attempts to improve the yields obtained by cyclisation of the above formyl derivatives and also of 2-formamido-3-picoline by the use of potassium *tert.*-butoxide (cf. Clemo and Swan, *loc. cit.*) have not met with success (cf. Tyson, *J. Amer. Chem. Soc.*, 1941, **63**, 2024; Marion and Ashford, *Candian J. Res.*, 1945, **23** B, 26).

None of the above-described azaindoles gave the Ehrlich or the pine-shaving reaction.

Experimental.

The picrates and benzoyl derivatives were prepared as described by Clemo and Swan (*loc. cit.*) unless otherwise stated.

4-*Amino*-3-*picoline.*—Thionyl chloride (8·8 c.c.) was cooled in ice, and dry β-picoline (5 c.c.) gradually added with shaking. After standing at room temperature for 6 days, the flask containing the dark red liquid was attached to a water-pump, and its temperature then gradually raised to 100°, and kept there for 1 hour. The residue was warmed with absolute alcohol (5 c.c.), which was then distilled off under reduced pressure (water-bath). The residue (a brown, sticky, deliquescent solid) was heated in a sealed tube with ammonium hydroxide (15 c.c., *d* 0·88) for 10 hours at 180—190°, the liquid evaporated to dryness on the water-bath, the residue dissolved in a little water, sodium hydroxide solution (40%) added, and the mixture distilled with superheated steam. The distillate was acidified (hydrochloric acid) and evaporated to dryness from the water-bath. The residue was dissolved in a small volume of water, basified (40% sodium hydroxide solution), and extracted with chloroform, the extract dried (K_2CO_3), the chloroform removed, and the residue recrystallised from benzene–light petroleum, giving the *base* (0·83 g.) as colourless needles, m. p. 108—109° (Found: C, 66·7; H, 7·6. $C_6H_8N_2$ requires C, 66·6; H, 7·5%). The *picrate* separated from methanol in bright yellow needles, m. p. 224—225°, after sintering at 217° (Found: C, 43·0; H, 3·25. $C_6H_8N_2,C_6H_3O_7N_3$ requires C, 42·75; H, 3·25%). The *benzoyl* derivative, prepared by the Schotten–Baumann method, separated from benzene–light petroleum as colourless plates, m. p. 122—123° (Found: C, 74·25; H, 5·65. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·65%). The m-*nitrobenzenesulphonyl* derivative, prepared by warming the base in acetone–pyridine with *m*-nitrobenzenesulphonyl chloride, distilling off the acetone, and adding water, separated from methanol (charcoal) as colourless plates, m. p. 198—199°, soluble in dilute sodium hydroxide solution, reprecipitated by dilute acetic acid (Found: C, 47·1; H, 4·2. $C_{12}H_{11}O_4N_3S,CH_3{\cdot}OH$ requires C, 48·0; H, 4·6%).

From some preparations, a *product* containing sulphur was isolated in yields up to 0·2 g.; this was more readily soluble in benzene than was 4-amino-3-picoline, and separated from light petroleum (b. p. 60—80°) as colourless prisms, m. p. 88—89° (Found: C, 67·1; H, 5·7; N, 13·4. $C_{12}H_{12}N_2S$ requires C, 66·65; H, 5·6; N, 13·0%). This could also be separated by fractional distillation at 15 mm., the fraction distilling below 160° consisting mainly of 4-amino-3-picoline, and that above 160° being mainly this by-product. This gave a *picrate*, which separated from acetone (in which it is very sparingly soluble) as bright yellow prisms, m. p. 233—235° (decomp.) (Found: C, 43·9; H, 2·85. $C_{12}H_{12}N_2S,C_6H_3O_7N_3$ requires C, 42·75; H, 2·7%). Attempts to prepare a benzoyl derivative (by the Schotten–Baumann method) and a *m*-nitrobenzenesulphonyl derivative failed. When a solution of the base in acetic acid was treated with one of potassium dichromate in dilute sulphuric acid for 1½ hours in the water-bath, no sign of reduction of the chromic acid was observed.

4-*Hydroxy*-3-*picoline.*—*Method* (1). β-Picoline (10 c.c.) was treated with thionyl chloride as described above, and the residue left after alcohol treatment was stirred with water (10 c.c.), filtered from insoluble matter, the filtrate heated in the water-bath for 1 hour with charcoal, filtered again, and heated in a sealed tube for 18 hours at 155°. Excess of sodium carbonate was added to the cooled liquid, which was then evaporated to a paste on the water-bath. The residue was extracted several times with 95% alcohol, the extract evaporated to dryness on the water-bath, the residue dissolved in absolute alcohol, evaporated to dryness under reduced pressure (water-bath), and the residue heated for 1 hour at 150°. The dark, viscous mass which remained on cooling was dissolved in chloroform, the solution boiled with charcoal, filtered, the filtrate concentrated, and to it, light petroleum was added, an oil then separating. The solvent layer was decanted, and the oil rubbed first with light petroleum, then with benzene, whereupon it solidified. The resulting solid was recrystallised from acetone (charcoal), giving 4-*hydroxy*-3-*picoline* (0·72 g., m. p. 95—98°), which after two further recrystallisations from acetone formed colourless prisms, m. p. 97—98°, after sintering at 92° (Found: C, 61·3; H, 7·1. $C_6H_7ON,\frac{1}{2}H_2O$ requires C, 61·0; H, 6·8%).

Method (2). To a solution of 4-amino-3-picoline (50 mg.) in 10% sulphuric acid (2 c.c.) at room

temperature, one of sodium nitrite (0·1 g.) in water (1·5 c.c.) was added, the mixture warmed for 15 minutes (water-bath), basified (sodium carbonate), the solution evaporated to dryness from the water-bath, the residue extracted with chloroform, the solvent removed from the extract, the residue rubbed with benzene, and the resulting solid filtered off and washed with benzene; 37 mg., m. p. 94—96°. When recrystallised from acetone, this gave colourless needles or prisms, m. p. 96—97°, after sintering at 92° (Found: C, 61·25; H, 6·7%). The m. p. was not depressed by admixture with the product obtained by method (1). The picrate separated from alcohol as yellow prisms, m. p. 206—207°. When the base (0·2 g.) was heated with ammonium hydroxide (2 c.c., *d* 0·88) and a trace of copper powder and copper sulphate in a sealed tube for 19 hours at 200°, 4-amino-3-picoline was re-formed.

4-Acetamido-3-picoline.—4-Amino-3-picoline (2·26 g.) was refluxed for 15 minutes with acetic anhydride (5 c.c.), and the mixture distilled under 15 mm., the product which distilled above 180° being a very viscous gum (2·78 g.) which rapidly crystallised. This was stirred with benzene, and the solid collected and washed with benzene, giving 1·73 g., m. p. 140—152°. This was sufficiently pure for the subsequent preparation, but for analysis a portion was recrystallised from benzene, giving colourless plates, m. p. 152—154° (Found: C, 64·25; H, 7·35. $C_8H_{10}ON_2$ requires C, 64·0; H, 6·7%).

2-Methyl-5-azaindole.—The above *acetyl* derivative (1·7 g.) was cyclised as described for the preparation of 2-methyl-7-azaindole (Clemo and Swan, *loc. cit.*). On distillation of the product, a considerable amount of 4-amino-3-picoline passed over first, and this was followed by a small amount of a high-boiling fraction, which solidified rapidly. The latter was recrystallised from benzene, giving *2-methyl-5-azaindole* (20 mg.) as almost colourless prisms, m. p. 208—209°, after sintering at 203° (Found: C, 72·6; H, 6·1. $C_8H_8N_2$ requires C, 72·75; H, 6·05%). The picrate was recrystallised first from alcohol, then from acetone, affording bright yellow needles, m. p. 213—214°, after sintering at 210°.

Improved Preparation of 2-Methylnicotinamide.—The following method gives a better yield than that described by Dornow (*Ber.*, 1940, **73**, 79). Ammonium hydroxide (86 c.c., *d* 0·88) was added to ethyl 2-methylnicotinate (8·6 g.), contained in a thick-walled bottle, and the mixture cooled in ice and saturated with ammonia. The bottle was then stoppered tightly and kept for 2 days at room temperature. On each of the next 5 successive days, the liquid was again saturated with ammonia at 0°, the ester layer gradually disappearing. The homogeneous liquid was then evaporated to dryness under reduced pressure (water-bath), and the residue recrystallised from a small volume of methanol (yield 5·92 g., *ca.* 84%).

Diacetyl Derivative of 3-Amino-2-picoline.—3-Amino-2-picoline (Dornow, *loc. cit.*) (1 g.) was refluxed for 15 minutes with acetic anhydride (2 c.c.), and the mixture distilled at 2 mm., the fraction of b. p. 125—140° (1·3 g.) being collected. This gum of the *diacetyl* derivative was used without further purification in the subsequent preparation, but for analysis, it was redistilled, the fraction of b. p. 125—127°/2 mm. being collected (Found: C, 62·7; H, 6·2. $C_{10}H_{12}O_2N_2$ requires C, 62·5; H, 6·2%). The *picrate* separated from alcohol as bright yellow needles, m. p. 155—156° after sintering at 146° (Found: C, 45·5; H, 3·7. $C_{10}H_{12}O_2N_2,C_6H_3O_7N_3$ requires C, 45·6; H, 3·6%).

2-Methyl-4-azaindole.—The above diacetyl derivative (0·9 g.) was subjected to the same cyclisation process as described previously, except that the duration of the reaction was only 10 minutes at 350°. After cooling, and addition of water, the product separated as a solid (0·6 g., m. p. 184—192°) which was filtered off, washed with water, dried, and recrystallised from benzene (in which it is very sparingly soluble), giving almost colourless prisms, m. p. 193—194° (Found: C, 73·3; H, 6·35. $C_8H_8N_2$ requires C, 72·75; H, 6·05%). The picrate separated from acetone as dark yellow prisms, m. p. 262° (decomp.).

4-Azaindole.—A mixture of anhydrous formic acid (0·45 c.c.) and acetic anhydride (1·1 c.c.) was heated at 50° for 2 hours, and the cooled solution added to a suspension of finely powdered 3-amino-2-picoline (1·05 g.) in dry ether (20 c.c.). An oil separated, but this gradually passed into solution. After standing for 4 days at room temperature the ether was removed, and the residue distilled, the formyl derivative being obtained as a gum (1·1 g., b. p. 145°/2 mm.). This gave a *picrate*, which separated from acetone–alcohol as bright yellow needles, m. p. 187—188° (Found: C, 43·35; H, 3·6. $C_7H_8ON_2,C_6H_3O_7N_3,\frac{1}{2}C_2H_6O$ requires C, 43·3; H, 3·6%). The above gum was treated with potassium ethoxide (prepared from potassium, 0·55 g.) for 30 minutes at 350°. After cooling, water was added and the product extracted with chloroform, the extract dried (K_2CO_3), the chloroform removed, and the residue recrystallised twice from benzene–light petroleum, and finally from benzene (charcoal), giving *4-azaindole* as colourless prisms, m. p. 127—128° (0·2 g.) (Found: C, 71·1; H, 5·6. $C_7H_6N_2$ requires C, 71·2; H, 5·1%). The *picrate* separated from acetone as bright yellow plates, m. p. 242—244° (decomp.) (Found: C, 46·0; H, 2·95. $C_7H_6N_2,C_6H_3O_7N_3,\frac{1}{2}C_3H_6O$ requires C, 46·25; H, 3·2%). The *benzoyl* derivative separated from benzene–light petroleum as colourless needles, m. p. 92—96° (Found: C, 75·1; H, 4·9. $C_{14}H_{10}ON_2$ requires C, 75·65; H, 4·5%).

4-Formamido-3-picoline.—4-Amino-3-picoline (0·65 g.) was formylated as described above for 3-amino-2-picoline. The resulting gum (0·69 g., b. p. 150°/2 mm.) set to a white solid. The *picrate* separated from alcohol as yellow needles, m. p. 199—200° (Found: C, 43·3; H, 3·75. $C_7H_8ON_2,C_6H_3O_7N_3,\frac{1}{2}C_2H_6O$ requires C, 43·3; H, 3·6%).

3-Acetomercuri-4-methylpyridine.—A mixture of 4-picoline (3·8 c.c.), mercuric acetate (1·6 g.), and water (0·7 c.c.) was heated in a sealed tube for 6 hours at 110°, the solution evaporated to dryness under reduced pressure (water-bath), and the residue extracted with hot benzene. On cooling, the extract deposited a solid, which was recrystallised from benzene, giving colourless plates, m. p. 148—150° (0·4 g.) (Found: N, 4·2. $C_8H_9O_2NHg$ requires N, 3·8%). Attempts to convert this into 3-bromo-4-methylpyridine were unsuccessful.

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50. *Studies in the Azole Series. Part III. The Interaction of Aminoacetonitrile and Carbon Disulphide.*

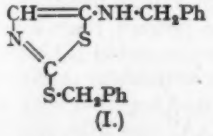
By A. H. Cook, Sir Ian Heilbron, and A. L. Levy.

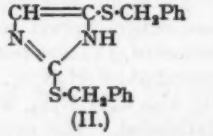
Pure aminoacetonitrile and carbon disulphide under selected neutral conditions give *5-amino-2-mercaptothiazole* (XI), whereas in presence of acetone the corresponding Schiff's *base* (XIII) is obtained. The compound (XI) is converted with remarkable ease into 2 : 4-*dithiohydantoin* (XIV), some derivatives of which can also be prepared by a more direct route, or into 2-*mercaptothiazol-5-one* (VI). Aminoacetonitrile and acetone condense to give 5-*imino*-2 : 2-*dimethyloxazolidine* (X) which readily suffers ring fission so that with carbon disulphide it afforded the *dithiocarbamic acid* derivative (IV); the latter was also formed by interaction of crude aminoacetonitrile and carbon disulphide under other conditions. The compound (IV) could also be converted into the mercaptothiazolone (VI) by the action of mineral acid.

In Part II of this series (*J.*, 1947, 1598) the reaction between α-aminonitriles and carbon disulphide was shown to lead generally and smoothly to 5-amino-2-mercaptothiazoles or to dithiohydantoins according to conditions. It was stated, however, that the behaviour of aminoacetonitrile in this connection was more complex, and the present paper is concerned more particularly with the intricacies of this reaction.

It is recorded (U.S.P. 2,143,816) that aminoacetonitrile and carbon disulphide afford dithiohydantoin, but reproduction of the conditions described gave, in our hands, a product which consisted chiefly of a brown resinous material with a crystalline substance as a minor constituent. Subsequently, the latter was recognised as 5-amino-2-mercaptothiazole (XI), a compound which was more conveniently prepared in other ways. It is noteworthy that the experiment in the above patent specifies the use of 2 molecular proportions of aminoacetonitrile, these proportions being employed in the case of other nitriles also. It seems likely that the inconclusiveness of the experiment in our hands, and incidentally the apparent divergence between the results described in the patent and those in this series of papers, are associated with the use of an excess of base, for what are indubitably the primary products, *i.e.*, 5-amino-2-mercaptothiazoles, have in several instances been shown to be susceptible of change under basic conditions. For this reason most of the following experiments employed at least 1 molecular proportion of carbon disulphide.

In preliminary experiments, aminoacetonitrile and carbon disulphide gave an exceedingly unstable compound which darkened eventually to a black powder on being worked up, though by simultaneous benzylation a small yield of a crystalline base, $C_{17}H_{16}N_2S_2$, was obtained. The latter liberated benzylthiol on treatment with alkali (*i.e.*, it contained at least one *S*-benzyl grouping) and two structures, (I) and (II), came into consideration. Later in this work


(I.)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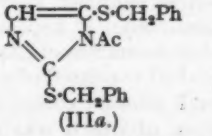
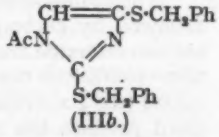
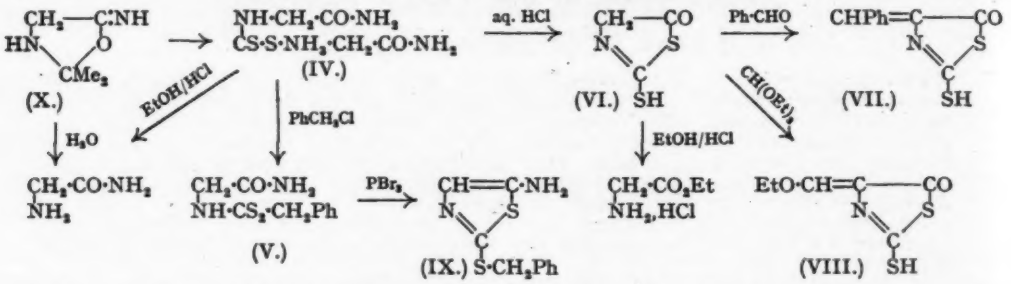

(IIIa.)


(IIIb.)

dithiohydantoin itself was obtained, and on benzylation afforded the above base, which must therefore be 2 : 4(5)-*dibenzylthioglyoxaline* (II). The exclusion of structure (I) was confirmed by the absorption spectrum of the base which differed markedly from all other 5-aminothiazoles studied (Parts I and II). The base gave a *monoacetyl* derivative which on being kept at just above its m. p. was converted into an *isomeride*, both compounds being hydrolysed under mild conditions to the original base; they are therefore formulated as (III*a*, *b*).

In view of these results attempts were made to carry out the reaction with free, or virtually free, nitrile in organic solvents. To this end aminoacetonitrile sulphate was titrated in ethanol suspension with sodium ethoxide. When the solution was treated with carbon disulphide, the product was pigmented and of indefinite properties. However, similar experiments in acetone suspension gave a compound, $C_8H_{12}O_2N_4S_2$, which for the following reasons was formulated as the *carbamylmethylammonium carbamylmethyldithiocarbamate* (IV). Aminoacetamide hydrochloride was produced by the action of ethanolic hydrogen chloride on it, and benzylation of the supposed dithiocarbamate gave *benzyl carbamylmethyldithiocarbamate* (V), which was also obtained directly from aminoacetamide. The compound (IV) possessed the notable property of being smoothly converted by cold dilute aqueous mineral acid into a compound, $C_3H_3ONS_2$, which was also obtained by acidifying an aqueous solution of the sodium

dithiocarbamate derived from aminoacetamide. The new compound afforded glycine ester hydrochloride on treatment with ethanolic hydrogen chloride and is formulated as 2-*mercapto*-



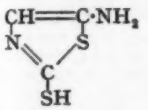
thiazol-5-one (VI), *S*-alkyl derivatives of which have previously been obtained in these laboratories in connection with work on penicillin by dehydrating dithiocarbamic esters of glycine. Formulation (VI) was confirmed by the ready condensation of the compound with benzaldehyde to give 2-*mercapto*-4-*benzylidenethiazol*-5-*one* (VII) and with ethyl orthoformate to yield 2-*mercapto*-4-*ethoxymethylenethiazol*-5-*one* (VIII). On acetylation the parent compound (VI) gave a *monoacetyl* derivative. Other potentialities of 2-mercaptothiazol-5-one, which is more conveniently prepared by another procedure described below, are being examined and will be reported separately. By contrast with the behaviour of the salt (IV), when the ester (V) was treated with phosphorus tribromide it lost the elements of water to give a *hydrobromide* of a base which was evidently 5-*amino*-2-*benzylthiothiazole* (IX). This reaction, which appears to be the first example of the formation of a 5-aminothiazole from an α-aminoamide, proceeded rapidly and quantitatively at room temperature.

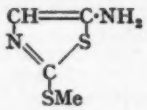
The mechanism of the formation of compound (IV) was revealed on keeping pure aminoacetonitrile in cold acetone with a trace of sodium ethoxide, whereupon a crystalline compound, $C_5H_{10}ON_2$ (*i.e.*, $NH_2{\cdot}CH_2{\cdot}CN + COMe_2$), separated. The latter, presumably 5-*imino*-2:2-*dimethyloxazolidine* (X) was evidently the intermediate by which the remarkably facile hydrolysis of the nitrile leading to (IV) was accomplished. Thus, when (X) was treated with cold water it gave aminoacetamide and acetone, when exposed to moist air it gave aminoacetamide carbonate (?) identical with the product obtained from aminoacetamide itself in air, and with ethanolic carbon disulphide it afforded the salt (IV) in excellent yield. The ease of formation of (X) is notable, and the generality of this kind of reaction is being studied. It is noteworthy that both compound (X) and aminoacetamide are formed in substantially quantitative yield, the latter being indeed most easily made by this means.

When aminoacetonitrile sulphate, suspended in acetone, was treated with sodium methoxide followed by carbon disulphide, it appeared that neutralisation was more prompt than with sodium ethoxide and that formation of (X) and hence of (IV) was practically eliminated. Under these conditions the product consisted of a compound (A) $C_6H_8N_2S_2$, whereas with slight modifications (see Experimental) another compound (B), also $C_6H_8N_2S_2$, was obtained together with a third product the nature of which was not elucidated. The compound (A) was also easily obtained from pure aminoacetonitrile, acetone, and carbon disulphide. On the other hand, when pure aminoacetonitrile was treated with carbon disulphide in ethyl acetate or other solvents so that any local excess of base was avoided, an excellent yield of a compound (C), $C_3H_4N_2S_2$, resulted. The last apparently contained both basic and pseudo-acidic groups, and behaved generally in the manner of 5-aminothiazoles. It was identical with the minor component of the mixture obtained according to U.S.P. 2,143,816 mentioned above, and is regarded as 5-*amino*-2-*mercaptothiazole* (XI). It afforded 5-*acetamido*-2-*mercaptothiazole*, which still dissolved in sodium hydroxide, and coupled, presumably in the 4-position, with diazonium salts. When the above condensation between aminoacetonitrile and carbon disulphide was effected in presence of methyl iodide a homologue of (XI), $C_4H_6N_2S_2$, was obtained. As this was basic but did not exhibit the pseudo-acidic properties of the thiazole (XI), it is best formulated as 5-*amino*-2-*methylthiothiazole* (XII). The thiazole (XI) condensed with acetone to give compound (A) (above), which must then be formulated as the acetone Schiff's *base* (XIII), these structures being compatible with the U.V. absorption of the compounds.

The thiazole (XI) exhibited notable reactivity in two other directions. On treatment with moderately concentrated mineral acid, it first passed into solution, to be replaced later by a precipitate of 2-mercaptothiazol-5-one (VI), this being the more direct route to that compound.

On the other hand, in cold aqueous alkali carbonate the product was a sensitive compound which was undoubtedly *dithiohydantoin* (XIV). It was characterised as its *diacetyl* derivative which


(XI.)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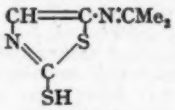
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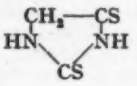
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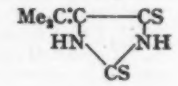
(XV).

readily lost its acetyl groups in sodium hydroxide but not in carbonate solution. Thus, when treated simultaneously with sodium hydroxide and benzyl chloride the acetyl derivative passed into the di-*S*-benzyl compound (II), which had been isolated in early exploratory experiments; this preparation was more satisfactory than direct benzylation of the dithiohydantoin (XIV) owing to the formation of intensely coloured products by that compound in alkaline solution. Incidentally, behaviour of this kind is exhibited by 4- but not by 2-thiohydantoin (Johnson and Chernoff, *J. Amer. Chem. Soc.*, 1912, **34**, 1208). The nature of the dithiohydantoin was conclusively demonstrated by its desulphurisation by means of Raney nickel to give glyoxaline, identified with an authentic specimen. Dithiohydantoin was a remarkably strong acid, liberating carbon dioxide from sodium hydrogen carbonate and even dissolving in aqueous sodium acetate though it was insoluble in water. Dithiohydantoin was also formed from compound (XI) by means of cold alcoholic potassium hydroxide or, in poorer yield, of cold aqueous alkali, being isolated in the former instance *via* a potassium salt. Treatment of the latter with methyl iodide led to methylation and quaternisation with the formation of the *methiodide* of 2-*methylthio*-4-*mercaptoglyoxaline*. The action of alcoholic sodium methoxide or pyridine on the thiazole (XI) gave changed products which, however, were not dithiohydantoin (as they did not give the characteristic acetyl derivative), nor was this compound obtained by the direct interaction of aminoacetonitrile and carbon disulphide in presence of pyridine, ammonia, or aqueous sodium carbonate. On the other hand, when the thiazole (XI) was warmed in pyridine in presence of acetone the sole product was compound (B) (above) which, having regard to its properties and the known rearrangement of 5-amino-2-mercaptothiazoles under similar conditions was formulated as 5-iso*propylidenedithiohydantoin* (XV).

The compound (XI) completely inhibited the growth of *Staphyllococcus aureus* at a dilution of 1 : 50,000, an activity comparable with that of the 4-methyl homologue (Part II, *loc. cit.*) and with that of other mercaptothiazoles (Gibbs and Robinson, *J.*, 1945, 925). In contrast, dithiohydantoin had no appreciable activity of this kind.

Experimental.

Reactions with Aminoacetonitrile Salts.—Aminoacetonitrile sulphate (30·8 g.) in water (50 c.c.) was treated with 20% potassium hydroxide until the solution was alkaline to brilliant-yellow, followed at 0° by potassium hydroxide (11 g.) in water (50 c.c.), carbon disulphide (15 g.), and benzyl chloride (25 g.), and the mixture shaken overnight. The deep brown liquid was extracted with ether, and the extract chromatographed in acetone–benzene (1 : 10) on alumina. The apparently homogeneous material from the eluate consisted of 2 : 4(5)-*dibenzylthioglyoxaline* and crystallised from aqueous methanol in colourless needles, m. p. 95° (Found : C, 65·5; H, 5·1; N, 8·9. $C_{17}H_{16}N_2S_2$ requires C, 65·4; H, 5·1; N, 9·0%). Light absorption (ethanol) : $\lambda_{max.}$ = 2570, 2640 A.; $E^{1\%}_{1\ cm.}$ = 275, 275. Acidification of the aqueous layer (above) gave benzyl *N*-carboxymethyldithiocarbamate, m. p. 163—165°. 2 : 4(5)-Dibenzylthioglyoxaline (3·2 g.), acetic anhydride (5 c.c.), and a few drops of sulphuric acid were warmed on the steam-bath for 5 mins. Evaporation and crystallisation from ethanol or benzene–light petroleum gave 1- or 3-*acetyl*-2 : 4-*dibenzylthioglyoxaline* as needles, m. p. 89—90° (Found : C, 64·3; H, 5·1; N, 8·4%). $C_{19}H_{18}ON_2S_2$ requires C, 64·4; H, 5·1; N, 7·9%). Light absorption (chloroform) : $\lambda_{max.}$ = 2600 A., $E^{1\%}_{1\ cm.}$ = 300; $\lambda_{inflex.}$ = 2800, $E^{1\%}_{1\ cm.}$ = 200. When the preceding compound was maintained at just above its m. p. for 30 mins. it resolidified. The *isomeride* crystallised from ethanol in well-formed plates, m. p. 99—100° (Found : C, 64·3; H, 5·1; N, 8·2%). Light absorption (chloroform) : $\lambda_{max.}$ = 2550, 3080A., $E^{1\%}_{1\ cm.}$ = 270, 135. When either of the above acetyl compounds was kept with ethanolic hydrogen chloride for several days it passed into solution and on evaporation a hydrochloride was obtained. Liberation of the free base in each case gave 2 : 4(5)-dibenzylthioglyoxaline, m. p. 95° undepressed by the original material.

A solution of sodium (4·9 g.) in ethanol (120 c.c.) was added during 2 hrs. to a fine, stirred suspension of aminoacetonitrile sulphate (26 g.) in acetone (150 c.c.) until neutral to phenolphthalein. Sodium sulphate was filtered off, and carbon disulphide (15 c.c.) added to the filtrate. The crystalline precipitate (6 g.) was removed, and a further crop (3·5 g.) obtained by diluting the mother-liquor with ether and keeping it overnight at 0°. Crystallisation of the combined deposit by adding ethanol or acetone to a solution in the minimum of water gave *carbamylmethylammonium carbamylmethyldithiocarbamate* (IV) (6·8 g.) as rectangular plates or needles, m. p. 139° (decomp.) (Found : C, 27·0; H, 5·6; N, 24·7; S, 28·6. $C_5H_{11}O_2N_4S_2$ requires C, 26·8; H, 5·4; N, 25·0; S, 28·6%). The compound (1·2 g.)

was obtained directly by adding carbon disulphide (1 c.c.) to a solution of aminoacetamide (1 g.) in acetone (30 c.c.). In one experiment with the nitrile sulphate, the acetone filtrates were evaporated and treated with ethanol–ether to give an unidentified *product* which crystallised from water in prismatic needles, m. p. 230—231° (decomp.) (Found: C, 38·9; H, 5·8; S, 26·2. $C_8H_{14}ON_4S_3$, *i.e.*, $2NH_2{\cdot}CH_2{\cdot}CN + CS_2 + COMe_2$, requires C, 39·0; H, 5·7; S, 26·0%).

The salt (IV) (2·0 g.) in water (10 c.c.) was shaken overnight with benzyl chloride (2 c.c.) in ether (10 c.c.). The product (1·4 g.; 65%) was *benzyl carbamylmethyldithiocarbamate* (V), which crystallised from toluene in feathery clusters of laths or from water in large plates, m. p. 119° (Found: C, 49·7; H, 5·4; N, 11·7; S, 26·9. $C_{10}H_{12}ON_2S_2$ requires C, 50·0; H, 5·0; N, 11·7; S, 26·7%). It was soluble in acetone or methanol, moderately soluble in ethyl acetate, and insoluble in ether; it was soluble without change in cold 2N-sodium hydroxide. This substance was obtained in poor yield by shaking aminoacetamide with carbon disulphide in 2N-sodium hydroxide and benzyl chloride in ether; the main product was benzyl *N*-carboxymethyldithiocarbamate, m. p. 164°, which was recovered on acidifying the aqueous layer. The original dithiocarbamic acid salt (1 g.) was refluxed for 5 mins. with acetic anhydride (5 c.c.), and the reagent then removed in a vacuum. The *product* (0·3 g.) crystallised in contact with water and recrystallised from ethanol in needles or small prisms, m. p. 176° (Found: C, 38·3; H, 3·8; S, 22·8. $C_8H_{10}O_2N_4S_2$ requires C, 37·8; H, 3·5; S, 22·4%). The salt (IV) (0·7 g.) was shaken with ethanolic hydrogen chloride (10 c.c.) for 20 mins. The crystalline form had changed, and the solid (0·65 g., 95%) consisted of aminoacetamide hydrochloride, which recrystallised from acetic acid in blades, m. p. 203—204° (decomp.) (Found: C, 22·1; H, 6·2. Calc. for $C_2H_7ON_2Cl$: C, 21·7; H, 6·3%); this compound was also prepared with the same m. p. by adding ethanolic hydrogen chloride to aminoacetamide in acetic acid, though Bergell and Wulfing (*Z. physiol. Chem.*, 1910, **64**, 353) quote the m. p. as 186—189°. The original salt (IV) (2·0 g.) in concentrated hydrochloric acid (5 c.c.) was cooled to 0° and diluted with water (10 c.c.), whereupon plates or clusters of small needles separated. *2-Mercaptothiazol-5-one* (VI) (1 g., 85%) recrystallised from benzene in bold needles which charred indefinitely above 300° (Found: C, 27·1; H, 2·3; N, 10·6. $C_3H_2ONS_2$ requires C, 27·1; H, 2·3; N, 10·5%). Light absorption (chloroform): $\lambda_{max.} = 2390$, 2800 A.; $E^{1\%}_{1cm.}$ 550, 1200. The compound dissolved in cold ethanol, methanol, acetone, ethyl acetate, or acetic acid, and in a large volume of hot benzene, chloroform, or ether. It gave an intense red-violet colour when treated with mild oxidising agents (*e.g.*, air, iodine, or ferric chloride) in presence of sodium acetate or bicarbonate but not in caustic alkali or dilute acid; the compound also discoloured easily on keeping. 2-Mercaptothiazol-5-one was also prepared by shaking together aminoacetamide (0·7 g.), potassium carbonate (1·4 g.), carbon disulphide (0·8 g.), and water (5 c.c.) for 5 hrs. at room temperature. The resulting solution was cooled and strongly acidified, the mercaptothiazolone (0·6 g.) being precipitated. A further preparation is described below.

When 2-mercaptothiazol-5-one (0·5 g.) was kept overnight with saturated ethanolic hydrogen chloride (10 c.c.), it slowly passed into solution, and needles (0·33 g.) of glycine ester hydrochloride, m. p. 148°, separated; addition of ether to the filtrate precipitated a further crop (total yield, 80%). The dithiocarbamate (IV) (1 g.) in water (6 c.c.) was treated with benzaldehyde (0·5 g.) and ethanol (3 c.c.) to give a homogeneous solution. Addition of concentrated hydrochloric acid (30 drops) gave a yellow crystalline precipitate of *2-mercapto-4-benzylidenethiazol-5-one* (0·2 g.), which recrystallised from ethanol in yellow needles, m. p. 211° (Found: C, 54·5; H, 3·3; N, 6·3. $C_{10}H_7ONS_2$ requires C, 54·3; H, 3·2; N, 6·3%). 2-Mercaptothiazol-5-one (0·75 g.), ethyl orthoformate (3 c.c.), and acetic anhydride (4 c.c.) were heated together on the steam-bath for 2 hrs.; the crystals (0·5 g.) were removed and washed with benzene. *2-Mercapto-4-ethoxymethylenethiazol-5-one* recrystallised from acetic acid in buff diamond-shaped needles, m. p. 209° (decomp.) (Found: C, 38·2; H, 4·0; N, 7·5; S, 33·55. $C_6H_7O_2NS_2$ requires C, 38·1; H, 3·7; N, 7·4; S, 33·9%). Light absorption (ethanol): $\lambda_{max.} = 2280$, 2790, 3450 A.; $E^{1\%}_{1cm.} = 260$, 600, ~ 1400.

It gave very intense colours with quinaldine methiodide, 2-methylbenzthiazole methiodide, 2-phenyloxazolone, etc., in ethanolic triethylamine. 2-Mercaptothiazol-5-one (1·3 g.), acetic anhydride (5 c.c.), and acetone (1 c.c.) were refluxed together for 45 mins. and excess of reagents removed in a vacuum. Rubbing the residue with water caused it to crystallise (yield, 1·3 g.), and the product was then distilled at 50° in high vacuum and finally crystallised from ether–light petroleum. The *monoacetyl* derivative of 2-mercaptothiazol-5-one formed pale yellow blades, m. p. 50° (Found: C, 34·4; H, 3·0; N, 7·9; S, 35·8. $C_5H_5O_2NS_2$ requires C, 34·3; H, 2·9; N, 8·0; S, 36·6%).

A suspension of aminoacetonitrile sulphate (13 g.) in acetone (60 c.c.) containing a little phenolphthalein was titrated with a solution of sodium (2·3 g.) in methanol (60 c.c.). Neutralisation was rapid (5 mins.) (cf. experiments in ethanol above), and after sodium sulphate had been filtered off, carbon disulphide (10 g.) was added to the filtrate. A red colour developed, and after 30 mins. yellow crystals (3·5 g.) of the acetone Schiff's *base* of 5-amino-2-mercaptothiazole were collected; the compound was best crystallised by chilling a solution in acetone under nitrogen, then separating as very pale cream laths, m. p. 167° (decomp.) (Found: C, 42·5; H, 4·9; N, 16·0; S, 37·4. $C_6H_8N_2S_2$ requires C, 41·9; H, 4·7; N, 16·3; S, 37·2%). The compound dissolved in aqueous sodium hydroxide and, in an inert atmosphere, the solution yielded a yellow powder, m. p. > 400°, on acidification. It was also changed on standing with dilute hydrochloric acid, yellow crystals of high m. p. being deposited.

Aminoacetonitrile sulphate (90 g.) was covered with methanol (400 c.c.) containing a trace of phenolphthalein, and a solution of sodium (16 g.) in methanol (400 c.c.) added during 40 mins. so that the mixture was permanently colourless. Sodium sulphate was filtered off, and the filtrate evaporated in a vacuum. The residual oily nitrile was dissolved in acetone (50 c.c.) and ether (50 c.c.) and treated with carbon disulphide (17 g.) under reflux. *5-iso*Propylidene-2 : 4-dithiohydantoin (see below), m. p. 235° (decomp.), separated in small bright orange needles (6 g.). The filtrate was treated with a further quantity (10 c.c.) of carbon disulphide, and after 2½ hrs. the acetone Schiff's base of 5-amino-2-mercaptothiazole (9 g.), m. p. 161° (decomp.), was removed. Dilution of the filtrate with water gave a product which recrystallised from water in colourless needles, m. p. 205° (decomp.) (Found: C, 42·6; H, 5·3; N, 20·5; S, 31·5%). The above substance (1 g.) was refluxed with 15% hydrochloric acid (10 c.c.)

for 1·5 hrs. Hydrogen sulphide was evolved, and on cooling a halogen-free solid separated; the compound crystallised from water in colourless rectangular prisms, m. p. 243° (decomp.) (Found: C, 41·05; H, 5·35; N, 11·6; S, 13·5%).

Reactions with Aminoacetonitrile.—Preparation. The following appears to be an improvement for large-scale work on that described in *Org. Synth.*, Coll. Vol. I, 298. Concentrated sulphuric acid (500 c.c.) was added during 30 mins. to ethanol (2·5 l.) stirred in a 5-l. flask with moderate cooling. Methyleneaminoacetonitrile (700 g.) (*Org. Synth.*, Coll. Vol. I, 355) was rapidly added to the solution at 45°. After 5—10 mins. crystals separated and were filtered off after a further hour's stirring, and washed with ethanol (1 l.). The product was dissolved in water (1 l.), and the solution run into stirred spirit (3 l.), the neutral sulphate (Found: equiv., 104. Calc.: 105), m. p. 177° (decomp.), being precipitated (655 g.). The filtrate deposited a further crop (70 g.) overnight (total yield 67%). The sulphate (180 g.) was finely powdered, covered with methanol (150 c.c.) containing a trace of phenolphthalein, and neutralised by adding a solution of sodium (32 g.) in methanol (800 c.c.) to the stirred mixture during 1 hour under nitrogen, so that the indicator remained permanently colourless. Sodium sulphate was filtered off and the filtrate evaporated at room temperature in a vacuum. Aminoacetonitrile (64 g. or 82% based on sodium used) distilled without decomposition at 65°/8 mm. and could be stored for several weeks at 0° under nitrogen without change.

Aminoacetonitrile (5 g.) in dry acetone (25 c.c.) was treated with 0·5 c.c. of a solution of sodium (0·1 g.) in ethanol (3·5 c.c.) at 0°. After 15 mins. the solid (9 g.; 90%) was collected; *5-imino-2 : 2-dimethyloxazolidine* crystallised best from dry acetone in bold prismatic needles, m. p. 101—102° (Found: C, 52·2; H, 8·6; N, 24·6. $C_5H_{10}ON_2$ requires C, 52·6; H, 8·8; N, 24·6%). The compound quickly deliquesced and after several days the syrup resolidified to a colourless substance, m. p. 126° (decomp.), which evolved carbon dioxide when treated with dilute mineral acid. The same substance was produced when aminoacetamide was exposed to moist air; Heintz (*Annalen*, 1868, **148**, 195) and Koenigs and Mylo (*Ber.*, 1908, **41**, 4429) noted this property of aminoacetamide but did not record the m. p. of the product. The oxazolidine (3 g.) was dissolved in water (5. c.c.) and the solution evaporated in a vacuum. The residue was dissolved in ethanol (50 c.c.), and carbon disulphide (1 c.c.) added. After standing overnight the salt (IV) (see above), m. p. 133—134° (decomp.) (2·8 g., 95%), was collected.

A solution of carbon disulphide (15 g.) in ethyl acetate (25 c.c.) was treated, with stirring, moderate cooling and in an atmosphere of nitrogen, with a solution of aminoacetonitrile (11 g.) in ethyl acetate (50 c.c.) added during 40 mins., and stirring continued for a further 30 mins. Dense granular yellow crystals of *5-amino-2-mercaptothiazole* (21·5 g., 82%) were collected and washed with ether. The compound darkened at 110° and melted only gradually up to about 230° (Found: N, 21·0. $C_3H_4N_2S_2$ requires N, 21·2%). Light absorption (methanol): $\lambda_{max.} = 2280, 3380$ A.; $E^{1\%}_{1cm.} = 340, 810$. It was difficult to recrystallise, was soluble in methanol, dilute alkali or acid, and moderately so in water, solutions discolouring easily on exposure to air. It gave the following colour reactions: (*a*) a chocolate-coloured precipitate with nitrous acid, (*b*) a black precipitate with bromine-water in neutral or acid solution, (*c*) a deep red colour with methanolic cinnamaldehyde in presence of hydrogen chloride, and (*d*) a deep purple colour with methanolic glyoxal in presence of triethylamine. In an experiment carried out according to U.S.P. 2,143,816 a small quantity of the above aminomercaptothiazole was obtained but none of the dithiohydantoin claimed; moreover, it seemed that the latter product was not present even in crude form in any substantial quantity, for various fractions of the product failed to give the acetyl derivative of the dithiohydantoin described below.

5-Amino-2-mercaptothiazole (1·3 g.), suspended in methanol (15 c.c.), was treated with acetic anhydride (2 c.c.). After a few moments the base passed into solution and its *acetyl* derivative (1·25 g.) separated. This recrystallised from water as colourless laths, m. p. 247° (decomp.) (Found: C, 34·8; H, 3·6; S, 36·8. $C_5H_6ON_2S_2$ requires C, 34·5; H, 3·5; S, 36·8%), which were sparingly soluble in organic solvents except pyridine, but dissolved in 2N-sodium hydroxide to give a solution which coupled smoothly with benzenediazonium chloride giving a crystalline purple dye. 5-Amino-2-mercaptothiazole (0·7 g.) was refluxed with acetone (40 c.c.) for 15 mins. under nitrogen; on standing, the filtered solution deposited the acetone Schiff's base, m. p. 166° (decomp.), described above, which was also prepared more conveniently as follows: Aminoacetonitrile (5 g.) was added to an ice-cold solution of carbon disulphide (7 c.c.) in acetone (25 c.c.). Heat was evolved and almost immediately the Schiff's base began to separate; after standing, it was collected (10·5 g., 70%) and the filtrate treated with acetone–ether (1 : 1) to give the unidentified material, m. p. 205° (decomp.), obtained from aminoacetonitrile sulphate above. 5-Amino-2-mercaptothiazole (1 g.) was kept for 1 hr. at room temperature in 2N-hydrochloric acid (25 c.c.). 2-Mercaptothiazolone (0·45 g., 45%), identical with that described above, was precipitated. Aminoacetonitrile sulphate (10·5 g.) was neutralised with sodium (2·1 g.) in methanol (55 c.c.) as in previous experiments, and the resulting solution of the base was kept at 0° overnight under nitrogen with carbon disulphide (80 g.) and methyl iodide (15 g.). The solution was evaporated to dryness in a vacuum, and the residue treated with ether (100 c.c.) and 2N-sodium hydroxide (25 c.c.). When the ethereal solution was dried, it slowly deposited crystals (ca. 2 g.). The *substance*, possibly 5-amino-2-methylthiothiazole, crystallised from ethanol in blunt, colourless rods, m. p. 152—153° (decomp.) (Found: C, 33·1; H, 4·2. $C_4H_6N_2S_2$ requires C, 32·9; H, 4·1%); it was soluble in dilute acid but insoluble in sodium hydroxide. Light absorption (N-hydrochloric acid): $\lambda_{inflex.} = 2510$ A., $E^{1\%}_{1cm.} = 750$; $\lambda_{max.} = 2800$ A., $E^{1\%}_{1cm.} = 1250$.

The benzyl ester (V) (1·7 g.) in dry ethyl acetate (25 c.c.) was treated with phosphorus tribromide (1 g.). *5-Amino-2-benzylthiothiazole hydrobromide* (2·5 g.) was immediately precipitated, and recrystallised from methanol–ether in prisms, m. p. 187° (decomp.) (Found: C, 39·6; H, 3·6; N, 9·2; S, 21·1. $C_{10}H_{11}N_2S_2Br$ requires C, 39·6; H, 3·6; N, 9·2; S, 21·1%). In methanol it gave the following reactions: (*a*) a chocolate-coloured precipitate with aqueous sodium nitrite, (*b*) yellow crystals on adding benzaldehyde, and (*c*) red-purple crystals on adding *p*-nitrosodimethylaniline; it gave no characteristic colour with glyoxal. The above hydrobromide was treated with aqueous sodium hydrogen carbonate, and the crude free base extracted with ether to give *5-amino-2-benzylthiothiazole*, crystallising from

*cyclo*hexane in colourless needles, m. p. 80° (Found : C, 54·2; H, 4·9; N, 12·4; S, 28·3. $C_{10}H_{10}N_2S_2$ requires C, 54·1; H, 4·5; N, 12·8; S, 28·8%). The ether-insoluble material melted at 180—181° (decomp.) after crystallisation from methanol and ether, but was not identified (Found : C, 45·4; H, 4·3; S, 18·3%).

5-Amino-2-mercaptothiazole (2·6 g.) and potassium hydroxide (1·2 g.) were kept in methanol (20 c.c.) under nitrogen for 2·5 hrs. Evaporation of the solvent left a clean crystalline residue of a potassium salt, which was dissolved in water (10 c.c.) and acidified with 2N-hydrochloric acid (15 c.c.) to give a yellow precipitate of 2 : 4-*dithiohydantoin* (1·8 g.), which was purified by precipitation with acid from its solution in sodium acetate (Found : C, 27·6; H, 3·5; S, 48·6. $C_3H_4N_2S_2$ requires C, 27·3; H, 3·0; S, 48·5%); it did not melt below 300°. Dithiohydantoin was a strong acid, being readily soluble in aqueous sodium acetate though almost insoluble in cold water. It readily discoloured, and alkaline solutions were prone to aerial oxidation. It was soluble in cold methanol, ethanol, acetone, or acetic acid, and in hot ethyl acetate or warm ether. Dithiohydantoin was also conveniently obtained by the following procedure : 5-amino-2-mercaptothiazole (19 g.) and potassium carbonate (23 g.) were kept in water (100 c.c.) under nitrogen for 9 hrs., and the solution acidified with 10% hydrochloric acid to precipitate the dithiohydantoin as a creamy yellow solid (15·5 g.).

Dithiohydantoin (1·2 g.) was refluxed in ethanol with Raney nickel (6·0 g.) for 15 mins. Removal of nickel sulphide and evaporation of the filtrate gave glyoxaline (0·2 g.), m. p. 90—91°, undepressed on admixture with an authentic specimen. Dithiohydantoin (8 g.) was refluxed with acetic anhydride (20 c.c.) for 10 mins. On cooling, the mass was washed out with water (100 c.c.) and recrystallised from toluene or benzene to give 1 : 3-*diacetyldithiohydantoin* (7·5 g.) as colourless needles, m. p. 161° (Found : C, 39·3; H, 3·8; N, 12·9; S, 29·7. $C_7H_8O_2N_2S_2$ requires C, 38·9; H, 3·7; N, 13·0; S, 29·6%). Light absorption (chloroform) : $\lambda_{max.} = 2670, 3210$ A.; $E^{1\%}_{1\,cm.} = 435, 465$.

It was soluble in most organic solvents except ether or hydrocarbons, and dissolved in sodium hydroxide undergoing deacetylation to regenerate dithiohydantoin. The acetyl derivative (0·9 g.) in 2N-sodium hydroxide (15 c.c.) was shaken overnight in an atmosphere of nitrogen with benzyl chloride (1·5 g.) in ether (10 c.c.). Evaporation of the ether left a crystalline residue of 2 : 4(5)-dibenzylthioglyoxaline (0·75 g.), identical with that obtained in earlier experiments.

The potassium salt of dithiohydantoin (obtained above) was treated with an excess of methyl iodide in methanol; a vigorous reaction occurred and potassium iodide separated. Evaporation of the solution left the *methiodide* of 4-*mercapto*-2-*methylthioglyoxaline*, which crystallised from acetone–ether in colourless spears, m. p. 136—138° (Found : C, 20·5; H, 3·0; N, 9·3. $C_5H_8N_2S_2I$ requires C, 20·8; H, 3·1; N, 9·7%). When 1 equiv. of methyl iodide was used, the crude monomethyldithiohydantoin was characterised as its *acetyl* derivative by warming with acetic anhydride. It crystallised from ethanol in colourless needles, m. p. 165° (Found : C, 38·7; H, 4·5; N, 14·7. $C_6H_8ON_2S_2$ requires C, 38·3; H, 4·3; N, 14·9%), and was readily hydrolysed to methylthiol. Light absorption (chloroform) : $\lambda_{max.} = 2420, 2580, 3230$ A.; $E^{1\%}_{1\,cm.} = 500, 500, 550$.

5-Amino-2-mercaptothiazole (1 g.) was covered with pyridine (5 c.c.) and acetone (2 c.c.), and the mixture boiled. Cooling to room temperature and dilution with water (10 c.c.) gave 5-iso*propylidene*-2 : 4-*dithiohydantoin* (0·5 g., 38%), which crystallised from pyridine–85% methanol in orange needles, m. p. 235° (decomp.) (Found : C, 42·2; H, 4·8; N, 15·9; S, 37·7. $C_6H_8N_2S_2$ requires C, 41·9; H, 4·7; N, 16·3; S, 37·2%). The same compound was obtained more conveniently as follows : Aminoacetonitrile (1·5 g.), pyridine (10 c.c.), and acetone (3 c.c.) were warmed together (steam-bath) while carbon disulphide (2 c.c.) was added. Cooling and addition of water gave the *iso*propylidene compound (1·25 g.).

We thank Dr. E. A. Braude for the absorption spectra and the Department of Scientific and Industrial Research for a grant to one of us (A. L. L.).

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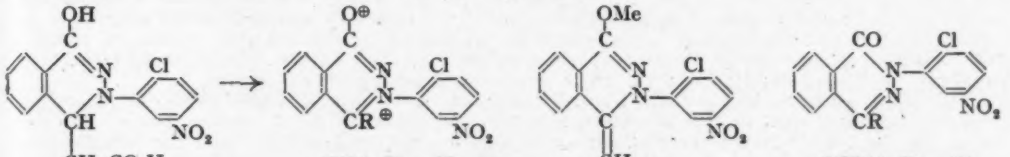
51. *A Reaction of Certain Diazosulphonates derived from β-Naphthol-1-sulphonic Acid. Part XXII. Derivatives of 2′-Chloro-5′-nitrobenzene-2-naphthol-1-diazosulphonate.*

By (the late) F. M. ROWE, A. T. PETERS, and Y. I. RANGWALA.

The presence of the *o*-chloro-substituent in sodium 1-(2′-chloro-5′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate causes such an increase in its resistance to fission in presence of aqueous sodium hydroxide that after reaction for 40 seconds only 5% of *sodium hydrogen* 3-(2′-*chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (I) is formed, with 90% of 2′-chloro-5′-nitrobenzeneazo-β-naphthol. With analogues containing no chlorine, the respective yields under similar conditions are 80% of the corresponding sodium salt and 9% of the azo-β-naphthol derivative. The properties of 1-*hydroxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (II) are compared with those of the unchlorinated analogue.

ACID hydrolysis of the sodium salt (I) gave the hydroxy-compound (II) which was converted by a mixture of boiling sulphuric and acetic acid or by acid dichromate into 2′-*chloro*-5′-*nitro*-3-*phenylphthalaz*-1-*one* (III) or the 4-*methyl* derivative (IV) of (III), in yields of 48·2% or 80·2%, respectively. The corresponding yields of the *m*-nitro-analogues were 56·5% and 59·1%

(cf. *J.*, 1928, 2556; 1931, 1918). Both (III) and (IV) possessed the expected properties. Methylation of (III) gave a product which combined with alcohols in varying proportions, like the analogous 2′ : 6′-dihalogeno-4′-nitro- and 2′-nitro-phenyl derivatives (cf. *J.*, 1931, 1073; 1935, 1796). With methyl sulphate in nitrobenzene, (IV) gave 74·7% of 1-*methoxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine* (V), although the corresponding derivative could not be prepared in the *m*-nitro-series. (V) gave water-soluble salts with mineral acids, and condensed with 2 : 4-dinitrochlorobenzene to yield 1-*methoxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine*.



(II.) (III.), R = H. (IV.), R = Me. (V.) (VIII.), R = H. (IX.), R = Me.

Oxidation of (II) with boiling aqueous potassium permanganate gave 1 : 4-*diketo*-3-(2′-*chloro*-5′-*nitrophenyl*)*tetrahydrophthalazine* (VI) in 40·4% yield, compared with a yield of 67% in the case of the *m*-nitro-analogue (cf. *J.*, 1935, 1808). Compound (VI) could not be methylated, but the methylene base (V) and *p*-nitrosodimethylaniline afforded 4-*keto*-1-*methoxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*, demethylated by hydrobromic acid (*d* 1·7) at 130° to (VI). Reduction of the nitro-compound (II) by iron powder and boiling aqueous-acetic acid gave 1-*hydroxy*-3-(2′-*chloro*-5′-*aminophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic acid* (VII), which was converted by a mixture of boiling sulphuric and acetic acid into 2′-*chloro*-5′-*amino*-3-*phenylphthalaz*-1-*one*. The corresponding 4-methyl derivative could not be obtained by acid dichromate oxidation of the amine (VII).

For comparison with the above phthalaz-1-ones, (III) and (IV), the isomeric 2′-*chloro*-5′-*nitro*-3-*phenylphthalaz*-4-*one* and its 1-*methyl* derivative, *viz.*, (VIII) and (IX), were synthesised in the usual manner (cf. *J.*, 1936, 311), and they possessed the expected properties; they did not form salts with mineral acids, and could not be methylated. Compound (III) and aqueous hydrochloric acid at 135° gave a substance, probably 1 : 4-*dihydroxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*, converted by the same reagent at 200° into a product of undetermined constitution. Isomerisation of 2′-chloro-5′-nitro-3-phenyl-4-methylphthalaz-1-one (IV) into 2′-chloro-5′-nitro-3-phenyl-1-methylphthalaz-4-one was effected by aqueous hydrochloric acid at 200°, but at 145° the reaction afforded 1 : 4-*dihydroxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine* (X), which was also obtained in one experiment by the action of acid dichromate on (II). Compound (X) is insoluble in aqueous mineral acids and alkalis, and could not be methylated, but aqueous hydrochloric acid at 180°, or warm concentrated sulphuric acid, converted it into 2′-chloro-5′-nitro-3-phenyl-1-methylphthalaz-4-one.

Experimental.

Sodium Hydrogen 3-(2′-*Chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-1-*sulphonate*-4-*acetate* (I).—A filtered solution of commercial 50% sodium β-naphthol-1-sulphonate (150 g.) in water (400 c.c.) was stirred rapidly at 0° into a solution of diazotised 2-chloro-5-nitroaniline, prepared by adding sodium nitrite (30 g.) to a cold suspension of the base (52 g.) in concentrated sulphuric acid (150 c.c.), and pouring the mixture on ice. The bright orange 2′-chloro-5′-nitrobenzene-2-naphthol-1-diazosulphonate, which separated immediately, was filtered off, washed with brine, mixed with cold water (100 c..), and sodium carbonate (100 g.) added quickly, with good stirring; a yellowish-brown suspension of sodium 1-(2′-chloro-5′-nitrobenzeneazo)-β-naphthaquinone-1-sulphonate was thus obtained. After 20 minutes, the suspension was added to a cold solution of sodium hydroxide (60 g.) in water (140 c.c.), with rapid stirring; the mixture became violet and then reddish-brown. After 48 hours it was acidified with hydrochloric acid, then made alkaline with sodium carbonate, and 2′-chloro-5′-nitrobenzeneazo-β-naphthol (6·8 g.) removed; the filtrate was reacidified and saturated with sodium chloride, and the acid *sodium* salt separated as an orange precipitate. Slow crystallisation (1 week) from alcohol gave orange prisms (32 g.; 23·8%, calc. on 2-chloro-5-nitroaniline) (Found: Cl, 8·35; S, 6·35. $C_{16}H_{11}O_7N_3ClSNa$ requires Cl, 7·9; S, 7·15%), readily soluble in water with a deep orange colour.

1-*Hydroxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (II).—A solution of the preceding sodium salt (5 g.) in water (500 c.c.) was boiled, and concentrated hydrochloric acid (20 c.c.) added gradually until evolution of sulphur dioxide had ceased. The *acid* (II) crystallised from acetic acid in colourless needles, m. p. 274° (3·5 g.; 86·6%) (Found: C, 53·4; H, 3·6; N, 11·8; Cl, 9·6. $C_{16}H_{12}O_5N_3Cl$ requires C, 53·1; H, 3·3; N, 11·6; Cl, 9·7%).

Derivatives of (II).—The *methyl* ester crystallised from methyl alcohol in pale yellow plates, m. p.

206° (Found : C, 54·1; H, 3·8; Cl, 9·6. $C_{17}H_{14}O_5N_3Cl$ requires C, 54·3; H, 3·7; Cl, 9·45%), insoluble in aqueous sodium carbonate. The *N*-methyl ether, *viz.*, 1-*keto*-3-(2′-*chloro*-5′-*nitrophenyl*)-2-*methyltetrahydrophthalazine*-4-*acetic acid*, crystallised from alcohol in pale yellow, rectangular plates, m. p. 267° (Found : C, 54·1; H, 4·05; N, 11·35; Cl, 9·25. $C_{17}H_{14}O_5N_3Cl$ requires C, 54·3; H, 3·7; N, 11·2; Cl, 9·45%), soluble in warm aqueous alkalis with a yellow colour. The *acetyl* derivative separated from alcohol in colourless prisms, m. p. 194° (Found : C, 53·4; H, 3·6; N, 10·5; Cl, 9·2. $C_{18}H_{14}O_6N_3Cl$ requires C, 53·5; H, 3·5; N, 10·4; Cl, 8·8%), and the *anilide* from aqueous acetic acid in irregular yellow prisms, m. p. 282° (Found : N, 12·7; Cl, 8·5. $C_{22}H_{17}O_4N_4Cl$ requires N, 12·8; Cl, 8·1%).

1-*Hydroxy*-3-(2′-*chloro*-5′-*aminophenyl*)-3 : 4-*dihydrophthalazine*-4-*acetic Acid* (VII).—Iron powder (5 g.) was added to a suspension of the nitro-compound (II) (5 g.) in boiling acetic acid (30 c.c.) and water (20 c.c.). After refluxing for 1 hour, the mixture was filtered and the filtrate added to cold water (300 c.c.); the precipitate was collected, extracted with warm aqueous sodium carbonate, the extract acidified, and the resulting *amine* crystallised from acetic acid in colourless prisms, m. p. 232—233° (decomp.) (1·8 g.; 36%) (Found : C, 57·5; H, 4·6; N, 11·7; Cl, 9·6. $C_{16}H_{14}O_3N_3Cl,0·5C_2H_4O_2$ requires C, 56·5; H, 4·4; N, 11·6; Cl, 9·8%), soluble in mineral acids and alkalis.

2′-*Chloro*-5′-*amino*-3-*phenylphthalaz*-1-*one*.—A solution of the above amine (VII) (5 g.) in concentrated sulphuric acid (10 c.c.) and acetic acid (10 c.c.) was boiled for 2 minutes, poured into cold water (100 c.c.), the mixture made alkaline with aqueous sodium hydroxide, and the *phthalaz*-1-*one* crystallised from pyridine in yellow prisms, m. p. 258° (decomp.) (3·1 g.; 75·7%) (Found : C, 61·8; H, 3·6; N, 15·1; Cl, 12·8. $C_{14}H_{10}ON_3Cl$ requires C, 61·9; H, 3·7; N, 15·4; Cl, 13·1%), soluble in dilute hydrochloric acid to give a colourless solution. The *acetyl* derivative crystallised from acetic acid in colourless prisms, m. p. 309—310° (decomp.) (Found : C, 61·3; H, 3·8; N, 13·4. $C_{16}H_{12}ON_3Cl$ requires C, 61·3; H, 3·8; N, 13·4%).

2′-*Chloro*-5′-*nitro*-3-*phenylphthalaz*-1-*one* (III).—A solution of 1-hydroxy-3-(2′-chloro-5′-nitrophenyl)-3 : 4-dihydrophthalazine-4-acetic acid (15 g.) in acetic acid (30 c.c.) and concentrated sulphuric acid (40 c.c.) was boiled for 2 minutes, added to water (250 c.c.), and the precipitated sulphate basified with aqueous ammonia. 2′-*Chloro*-5′-*nitro*-3-*phenylphthalaz*-1-*one* crystallised from methyl alcohol in pale yellow needles, m. p. 255° (6 g.; 48·2%) (Found : C, 55·6; H, 3·0; N, 13·9; Cl, 11·8. $C_{14}H_8O_3N_3Cl$ requires C, 55·7; H, 2·65; N, 13·9; Cl, 11·8%), which formed water-soluble salts with mineral acids. The *picrate* crystallised from alcohol in yellow prisms, m. p. 222° (Found : C, 45·6; H, 2·4; N, 15·9. $C_{20}H_{11}O_{10}N_6Cl$ requires C, 45·2; H, 2·1; N, 15·8%). Attempted reduction of the nitro-compound (II) with aqueous sodium sulphide gave a resin.

Compound (II), alone or in nitrobenzene, was heated with excess of methyl sulphate at 100° for 1 hour, giving a product which combined with alcohols in indefinite proportions, and crystallised from ethyl alcohol in yellow prisms, m. p. 198° (decomp.), or from methyl alcohol in greenish-yellow prisms, m. p. 192° (decomp.).

2′-*Chloro*-5′-*nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one* (IV).—(*a*) A solution of powdered (II) (10 g.) in concentrated sulphuric acid (100 c.c.) was added to a cold solution of potassium dichromate (4 g.) in water (400 c.c.), and the mixture heated to 80°; after 1 hour at this temperature, the precipitate was collected, basified with aqueous ammonia, and crystallised from methyl alcohol in pale yellow, rectangular prisms, m. p. 244° (7 g.; 80·2%) (Found : C, 57·1; H, 3·4; N, 13·3; Cl, 11·1. $C_{15}H_{10}O_3N_3Cl$ requires C, 57·05; H, 3·2; N, 13·3; Cl, 11·2%). 2′-*Chloro*-5′-*nitro*-3-*phenyl*-4-*methylphthalaz*-1-*one* forms water-soluble salts with mineral acids, and the *picrate* separated from alcohol in yellow prismatic needles, m. p. 234° (Found : C, 46·5; H, 2·3; N, 15·7. $C_{21}H_{12}O_{10}N_6Cl$ requires C, 46·3; H, 2·4; N, 15·4%).

(*b*) Compound (II) (2 g.) and nitric acid (*d* 1·5; 5 c.c.) at 0° for 5 minutes gave (IV), m. p. and mixed m. p. 244° (1 g.; 57·2%).

1-*Methoxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-4-*methylene*-3 : 4-*dihydrophthalazine* (V) *and its Derivatives*.—Methylation of the phthalazone (IV) (4·5 g.) in nitrobenzene (30 c.c.) with methyl sulphate (3 g.), at 110—115° for 1 hour, gave the *methylene* compound (V), which crystallised from alcohol in orange-red rectangular plates, with a coppery reflex, m. p. 142° (3·9 g.; 74·7%) (Found : C, 58·6; H, 3·7; Cl, 10·9; OMe, 9·65. $C_{16}H_{12}O_3N_3Cl$ requires C, 58·3; H, 3·6; Cl, 10·8; OMe, 9·4%). The *perchlorate* crystallised from dilute acetic acid containing a little perchloric acid in colourless needles, m. p. 224° (Found : Cl, 16·9. $C_{16}H_{13}O_7N_3Cl_2$ requires Cl, 16·5%).

The methylene base (1 g.) and *p*-nitrosodimethylaniline (0·5 g.), refluxed in alcohol (30 c.c.) for 1 hour, gave 4-*keto*-1-*methoxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*, which crystallised from alcohol in sand-coloured prisms, m. p. 170° (0·6 g.; 59·4%) (Found : C, 54·0; H, 3·0; N, 12·8; Cl, 10·5. $C_{15}H_{10}O_4N_3Cl$ requires C, 54·3; H, 3·0; N, 12·7; Cl, 10·7%), insoluble in aqueous mineral acids and alkalis and demethylated by hydrobromic acid (*d* 1·7) at 130° to 1 : 4-diketo-3-(2′-chloro-5′-nitrophenyl)tetrahydrophthalazine (VI), m. p. 282° (see later). Compound (V) (1 g.) condensed with 2 : 4-dinitrochlorobenzene (0·7 g.) in boiling alcohol (50 c.c.) in presence of potassium acetate (2 g.) (1·5 hours) to yield 1-*methoxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-4-(2″ : 4″-*dinitrobenzylidene*)-3 : 4-*dihydrophthalazine*, which crystallised from alcohol in cherry-red needles, m. p. 285° (1 g.; 66·5%) (Found : C, 52·8; H, 3·0; N, 14·4. $C_{23}H_{14}O_7N_5Cl$ requires C, 53·3; H, 2·8; N, 14·1%), and formed a colourless solution with dilute hydrochloric acid.

1 : 4-*Diketo*-3-(2′-*chloro*-5′-*nitrophenyl*)*tetrahydrophthalazine* (VI).—Powdered potassium permanganate (15 g.) was added gradually during 10 minutes to a suspension of (II) (20 g.) in water (300 c.c.) at 80°. The mixture was then boiled for 1 minute, filtered, the filtrate acidified with hydrochloric acid, and the precipitate crystallised from acetic acid in colourless prisms, m. p. 282°, of the *diketo*-compound (7·1 g.; 40·4%) (Found : C, 52·8; H, 3·0; N, 13·1. $C_{14}H_8O_4N_3Cl$ requires C, 52·9; H, 2·5; N, 13·2%), which could not be methylated by the action of methyl iodide on its silver salt in dry methyl alcohol or benzene.

2′-*Chloro*-5′-*nitro*- *and* -5′-*amino*-3-*phenylphthalaz*-4-*one*.—On refluxing a solution of phthalaldehydic acid (1·5 g.) and 2-chloro-5-nitrophenylhydrazine (1·5 g.) in alcohol (50 c.c.) for 10 minutes, orange

needles of o-*carboxybenzaldehyde* 2-*chloro*-5-*nitrophenylhydrazone*, m. p. 252°, separated (2·2 g.; 86·3%) (Found: C, 52·5; H, 3·2; N, 12·9. $C_{14}H_{10}O_4N_3Cl$ requires C, 52·6; H, 3·1; N, 13·1%), soluble in warm aqueous alkalis with a yellow colour. Warm concentrated sulphuric acid converted the carboxylic acid into 2′-*chloro*-5′-*nitro*-3-*phenylphthalaz*-4-*one* (95% yield), which crystallised from aqueous alcohol in colourless prisms, m. p. 164° (softens from 150°) (Found: C, 56·1; H, 2·7; N, 13·6; Cl, 11·4. $C_{14}H_8O_3N_3Cl$ requires C, 55·7; H, 2·65; N, 13·9; Cl, 11·8%), insoluble in dilute mineral acids and alkalis. It was reduced by boiling aqueous-alcoholic sodium sulphide to the corresponding *amine* (43·6% yield), which crystallised from alcohol–light petroleum in colourless needles, m. p. 160° (Found: N, 15·3. $C_{14}H_{10}ON_3Cl$ requires N, 15·5%); the *acetyl* derivative crystallised from the same solvent in colourless rhombs, m. p. 247° (Found: N, 13·4. $C_{16}H_{12}O_2N_3Cl$ requires N, 13·4%).

2′-*Chloro*-5′-*nitro*- and -*amino*-3-*phenyl*-1-*methylphthalaz*-4-*one*.—Alcoholic solutions of acetophenone-o-carboxylic acid (4 g.) and 2-chloro-5-nitrophenylhydrazone (4 g.), refluxed for 10 minutes, gave o-*carboxyacetophenone* 2-*chloro*-5-*nitrophenylhydrazone*, which separated in yellow cubes, m. p. 160° (4·5 g.; 63·2%) (Found: C, 53·6; H, 3·4; N, 12·3. $C_{15}H_{12}O_4N_3Cl$ requires C, 54·0; H, 3·6; N, 12·6%). On being heated at 135°, or more conveniently by being refluxed with acetic acid (40 c.c.) for 1 hour, the hydrazone (1 g.) was converted into 2′-*chloro*-5′-*nitro*-3-*phenyl*-1-*methylphthalaz*-4-*one*, which separated from aqueous acetic acid in colourless rhombs, m. p. 163° (0·8 g.; 83·1%) (Found: C, 56·6; H, 3·0; N, 13·6; Cl, 11·3. $C_{15}H_{10}O_3N_3Cl$ requires C, 57·05; H, 3·2; N, 13·3; Cl, 11·2%). It was also obtained in 67% yield by heating 2′-chloro-5′-nitro-3-phenyl-4-methylphthalaz-1-one with aqueous hydrochloric acid (8 : 1) in a sealed tube at 200° for 6 hours. Reduction with boiling aqueous-alcoholic sodium sulphide for 20 minutes afforded 2′-*chloro*-5′-*amino*-3-*phenyl*-1-*methylphthalaz*-4-*one* (27·5%), which crystallised from aqueous alcohol in colourless cubes, m. p. 145° (Found: C, 62·8; H, 4·2; N, 14·4; Cl, 12·5. $C_{15}H_{12}ON_3Cl$ requires C, 63·0; H, 4·2; N, 14·7; Cl, 12·4%). The *acetyl* derivative crystallised from aqueous alcohol in colourless cubes, m. p. 238° (Found: N, 12·6. $C_{17}H_{14}O_2N_3Cl$ requires N, 12·8%).

Action of Dilute Hydrochloric Acid on 2′-*Chloro*-5′-*nitro*-3-*phenylphthalaz*-1-*one*.—The phthalaz-1-one (1·5 g.) was heated with dilute hydrochloric acid (1 : 8; 18 c.c.) in a sealed tube at 135° for 3 hours. The product, probably 1 : 4-*dihydroxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-3 : 4-*dihydrophthalazine*, crystallised from aqueous alcohol in yellow needles, m. p. 225—227° (1·1 g.; 69·3%) (Found: C, 54·4; H, 3·2; N, 12·9; Cl, 10·8. $C_{14}H_{10}O_4N_3Cl$ requires C, 52·6; H, 3·1; N, 13·1; Cl, 11·1%), and was converted (as also was 2′-chloro-5′-nitro-3-phenylphthalaz-1-one) by dilute hydrochloric acid (1 : 8) in a sealed tube at 200° into a *product*, which crystallised from methyl alcohol in colourless rhombs, m. p. 156° (Found: C, 56·1; H, 2·9; N, 13·5; Cl, 11·7. $C_{14}H_9O_3N_3Cl$ requires C, 55·7; H, 2·65; N, 13·9; Cl, 11·8%). The constitution of this is uncertain, and, on admixture with 2′-chloro-5′-nitro-3-phenylphthalaz-4-one, the m. p. was depressed.

1 : 4-*Dihydroxy*-3-(2′-*chloro*-5′-*nitrophenyl*)-4-*methyl*-3 : 4-*dihydrophthalazine*.—2′-Chloro-5′-nitro-3-phenyl-4-methylphthalaz-1-one (1·5 g.) was heated with dilute hydrochloric acid (1 : 8; 18 c.c.) in a sealed tube at 145° for 5 hours. The *dihydroxy*-compound crystallised from methyl alcohol in pale yellow prismatic needles, m. p. 238° (1·3 g.; 83%) (Found: C, 53·7; H, 3·6; N, 12·4; Cl, 10·6. $C_{15}H_{12}O_4N_3Cl$ requires C, 54·0; H, 3·6; N, 12·6; Cl, 10·6%), converted by heating with dilute hydrochloric acid (1 : 8) in a sealed tube at 180° for 3 hours, or by warming with concentrated sulphuric acid for 10 minutes, into 2′-chloro-5′-nitro-3-phenyl-1-methylphthalaz-4-one, m. p. and mixed m. p. 163°.

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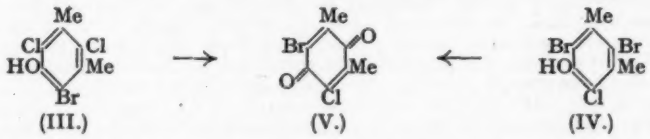
52. *Halogenation of* m-5- *and* m-2-*Xylenol. Mixed Chlorobromo-derivatives.*

By S. W. GLEED and A. T. PETERS.

For the purpose of comparison with the degradation products of certain polyhalogeno-*m*-xylenols, eight new mixed *chlorobromo*-m-*xylenols* are prepared. 4-*Chloro*-6-*bromo*-m-*xyloquinone* is characterised.

THE only mixed halogeno-*m*-xylenol described in the literature is 2-chloro-4 : 6-dibromo-*m*-5-xylenol (Lesser and Gad, *Ber.*, **1923**, **56**, 963), prepared by dibrominating 2-chloro-*m*-5-xylenol. The quick monobromination method, using chloroform as solvent and aluminium bromide as catalyst, and used to prepare 2-bromo-4-nitroaniline (*J.*, **1935**, 1135), was applied successfully to the preparation in almost theoretical yield of 2-*chloro*-4-*bromo*-m-5-*xylenol* (I) from 2-chloro-*m*-5-xylenol. The usual methods of bromination gave mixtures of 2-chloro- and 2-chloro-4 : 6-dibromo-derivatives. A similar monochlorination, using iodine as catalyst, of 2-bromo-*m*-5-xylenol, gave 4-*chloro*-2-*bromo*-m-5-*xylenol* (II). 2-Chloro-4 : 6-dibromo-*m*-5-xylenol was obtained by further bromination of (I), and the 4 : 6-*dichloro*-2-*bromo*-derivative was prepared by chlorination in chloroform of (II), or by dichlorinating 2-bromo-*m*-5-xylenol in acetic acid. 2 : 6-*Dichloro*-4-*bromo*-m-5-*xylenol* (III) was prepared readily by monobrominating 2 : 4-di-

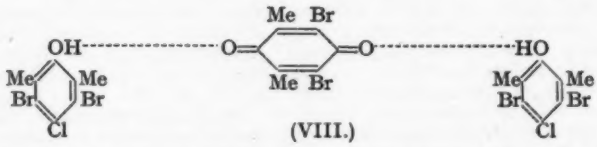
chloro-*m*-5-xylenol, or by the monochlorination of (I), whilst bromination of (II) gave 4-*chloro*-2 : 6-*dibromo*-m-5-*xylenol* (IV). Each of the two last-named mixed trihalogeno-derivatives is oxidised by nitric acid to 4-*chloro*-6-*bromo*-m-*xyloquinone* (V) :



(III.) (V.) (IV.)

It is noteworthy that 2 : 4 : 6-tribromo-, m. p. 165—166°, 2-chloro-4 : 6-dibromo-, m. p. 164°, and 2 : 6-dichloro-4-bromo-*m*-5-xylenol, m. p. 165—166°, do not depress the m. p. of one another.

5-*Chloro*-4-*bromo*-m-2-*xylenol* (VI) was prepared in almost theoretical yield from 5-chloro-*m*-2-xylenol by the quick monobromination method; on adding (VI) to excess of liquid bromine, 5-*chloro*-4 : 6-*dibromo*-m-2-*xylenol* (VII), m. p. 188—189°, was formed, which was also obtained by a similar bromination of 5-chloro-*m*-2-xylenol. On adding aqueous bromine to compound (VII) at room temperature, 4 : 6-dibromo-*m*-xyloquinone was obtained, together with a scarlet adduct (VIII) of the quinhydrone type, formed from 1 mol. of the above quinone and 2 mols. of compound (VII). The constitution of this product was confirmed by synthesis.



(VIII.)

4 : 5-*Dichloro*-6-*bromo*-m-2-*xylenol* (IX), m. p. 186—188°, was prepared by adding molten 4 : 5-dichloro-*m*-2-xylenol to excess of liquid bromine, but no mixed nuclear halogeno-*m*-2-xylenol was isolable by attempted chlorination of 5-bromo-*m*-2-xylenol. In chloroform at 5—15°, only an intractable oil was obtained, whilst more vigorous chlorination of 5-bromo-*m*-2-xylenol caused some displacement of bromine.

Improved methods were devised for the preparation of 5-bromo-, 4 : 5-dibromo-, and 4 : 5 : 6-tribromo-*m*-2-xylenol (X) (cf. Auwers and Markovitz, *Ber.*, 1908, **41**, 2336) by the direct bromination of *m*-2-xylenol. In contrast to the halogeno-*m*-5-xylenols, the third bromine atom is difficult to introduce, compound (X) being obtained by adding *m*-2-xylenol to a large excess of bromine.

In view of the similarities in m. p. and the tendency to show no depression on admixture of mixed halogeno-derivatives, it was imperative to control constitution by full analysis, and as far as possible by using only the requisite molecular proportion of halogen; *e.g.*, in preparing 2 : 6-dichloro-4-bromo-*m*-5-xylenol from 2 : 6-dichloro-*m*-5-xylenol, only 1 mol. of bromine was used, and the resulting product was shown to contain three halogen atoms. Replacements of one halogen by another were thus carefully controlled.

Experimental.

2-*Chloro*-4-*bromo*-m-5-*xylenol* (I).—Bromine (20·5 g.; 1 mol.) in dry chloroform (100 c.c.) was added rapidly to a stirred mixture of 2-chloro-*m*-5-xylenol (20 g.; 1 mol.), dry chloroform (200 c.c.), and a little anhydrous aluminium bromide. A vigorous reaction was complete in a few seconds, and, after removal of solvent, 2-*chloro*-4-*bromo*-m-5-*xylenol* was crystallised from light petroleum; it formed colourless needles, m. p. 68° (yield, 29 g.; 96·3%) (Found: C, 41·3; H, 3·5; 0·2715 g. gave 0·3829 g. of AgCl + AgBr. C_8H_8OClBr requires C, 40·8; H, 3·4%; AgCl + AgBr, 0·3822 g.). Its constitution was further established by bromination to 2-chloro-4 : 6-dibromo-*m*-5-xylenol.

4-*Chloro*-2-*bromo*-m-5-*xylenol* (II).—Solutions of 2-bromo-*m*-5-xylenol (20 g.; 1 mol.) in dry chloroform containing a few crystals of iodine, and chlorine (7·1 g.; 1 mol.) in the same solvent (100 c.c.), were mixed rapidly. 4-*Chloro*-2-*bromo*-m-5-*xylenol* separated from light petroleum in colourless needles, m. p. 90—110°, softening at 83° (yield, 18·2 g.; 77·4%) (Found: C, 40·85; H, 3·5; total halogen, 49·7. C_8H_8OClBr requires C, 40·8; H, 3·4; total halogen, 49·05%).

2-*Chloro*-4 : 6-*dibromo*-m-5-*xylenol*.—Bromine (103 g.; 2 mols.) in acetic acid (200 c.c.) was added to a solution of 2-chloro-*m*-5-xylenol (50 g.; 1 mol.) in the same solvent (600 c.c.) during 3 hours, with stirring. After addition to water, the precipitate was collected; it crystallised from light petroleum in long, colourless needles, m. p. 164° (yield, 88 g.; 87·5%) (Found: C, 32·0; H, 2·4; 0·1135 g. gave 0·1886 g. of AgCl + AgBr. Calc. for $C_8H_7OClBr_2$: C, 30·5; H, 2·2%; AgCl + AgBr, 0·1875 g.) (cf. Lesser and Gad, *loc. cit.*). It was oxidised by nitric acid (*d* 1·42) at 100° for 10 minutes to 4 : 6-dibromo-

m-xyloquinone, golden-yellow plates, m. p. 172° (Kohn and Feldmann, *Monatsh.*, 1928, **49**, 169, record m. p. 169°).

4 : 6-*Dichloro*-2-*bromo*-m-5-*xylenol*.—Compound (II) was treated with a further mol. of chlorine as above; the *dichlorobromo*-derivative crystallised from light petroleum in long, colourless needles, m. p. 182°, in almost theoretical yield (Found: C, 35·3; H, 2·8; total halogen, 56·2. $C_8H_7OCl_2Br$ requires C, 35·55; H, 2·6; total halogen, 55·9%). Larger amounts were prepared by adding chlorine (37 g.; 2 mols.) in acetic acid (500 c.c.), slowly and with good agitation, to a cooled solution of 2-bromo-*m*-5-xylenol (52 g.; 1 mol.) in acetic acid (500 c.c.), and diluting the mixture (yield, 61 g.; 87%).

2 : 6-*Dichloro*-4-*bromo*-m-5-*xylenol*.—(*a*) Chlorine (4·5 g.; 1 mol.) in acetic acid (150 c.c.) was added slowly to a solution of (I) (15 g.; 1 mol.) in acetic acid (120 c.c.) at <20°. After dilution, the precipitate was collected; it crystallised from light petroleum in long, colourless needles, m. p. 165—166° (yield, 16·8 g.; 97·6%) (Found: C, 35·8; H, 2·8; 5·014 mg. gave 8·940 mg. of AgCl + AgBr. $C_8H_7OCl_2Br$ requires C, 35·55; H, 2·6%; AgCl + AgBr, 8·821 mg.). 2 : 6-*Dichloro*-4-*bromo*-m-5-*xylenol* was oxidised by nitric acid (*d* 1·42) at 100° to 4-*chloro*-6-*bromo*-m-*xyloquinone*, which crystallised from light petroleum in large yellow plates, m. p. 170—171° (Found: 4·693 mg. gave 6·215 mg. AgCl + AgBr. $C_8H_5O_2ClBr$ requires AgCl + AgBr, 6·235 mg.).

(*b*) Bromine (10 g.; 1 mol.) in acetic acid (80 c.c.) was added slowly, with stirring, to a solution of 2 : 4-dichloro-*m*-5-xylenol (12 g.; 1 mol.) in acetic acid (120 c.c.) at room temperature. Next day, the mixture was added to water (500 c.c.); yield, 14·4 g. (84·7%).

4-*Chloro*-2 : 6-*dibromo*-m-5-*xylenol*.—Bromine (10 g.; 1 mol.) in acetic acid (100 c.c.) was added slowly to a solution of compound (II) (14·7 g.; 1 mol.) in the same solvent at below 20°. After 1 hour, the mixture was poured on ice–water (600 g.); the *chloro-dibromo*-compound crystallised from light petroleum in long, colourless needles, m. p. 170° (yield, 18 g.; 90%) (Found: C, 30·1; H, 2·4; 4·618 mg. gave 7·515 mg. of AgCl + AgBr. $C_8H_7OClBr_2$ requires C, 30·5; H, 2·2%; AgCl + AgBr, 7·628 mg.). Oxidation as above gave 4-chloro-6-bromo-*m*-xyloquinone.

5-*Chloro*-4-*bromo*-m-2-*xylenol* (VI).—Bromine (16·8 g.; 1 mol.) in dry chloroform (75 c.c.) was added rapidly to 5-chloro-*m*-2-xylenol (15 g.; 1 mol.) in chloroform (150 c.c.), in presence of a little aluminium bromide, and the mixture kept at 50° for 2 hours. The *compound* (VI) formed fine colourless needles, m. p. 86—87°, from light petroleum (yield, 21·8 g.; 96·6%) (Found: 2 mg. gave 2·812 mg. of AgCl + AgBr. C_8H_8OClBr requires 2·815 mg. AgCl + AgBr).

5-*Chloro*-4 : 6-*dibromo*-m-2-*xylenol* (VII).—(*a*) Molten 5-chloro-4-bromo-*m*-2-xylenol (2·3 g.; 1 mol.) was added in small quantities to liquid bromine (7·4 g.; 4·5 mols.) during 15 minutes at room temperature. Compound (VII) crystallised from chloroform in almost colourless, prismatic needles, m. p. 188—189° (yield, 3·05 g.; 96·9%) (Found: 2 mg. gave 3·21 mg. of AgCl + AgBr. $C_8H_7OClBr_2$ requires AgCl + AgBr, 3·33 mg.). Bromine (2 mols.) in twelve times its weight of water was added to finely-ground 5-*chloro*-4 : 6-*dibromo*-m-2-*xylenol* at room temperature, to give 4 : 6-dibromo-*m*-xyloquinone and an adduct (VIII) of the same quinone (1 mol.) and 5-chloro-4 : 6-dibromo-*m*-2-xylenol (2 mols.), which crystallised from dry chloroform in scarlet, prismatic needles, m. p. 141—142°; its constitution was confirmed by synthesis, by melting the requisite proportions of the two constituents and crystallising.

(*b*) Finely-ground 5-chloro-*m*-2-xylenol (10·5 g.; 1 mol.) was added gradually to liquid bromine (43 g.; 4 mols.) at 20° during 1 hour; yield, 20·7 g. (98·5%).

4 : 5-*Dichloro*-6-*bromo*-m-2-*xylenol* (IX).—Molten 4 : 5-dichloro-*m*-2-xylenol (5·75 g.; 1 mol.) was added gradually to liquid bromine (19·3 g.; 4 mols.) at room temperature. The *compound* (IX) crystallised from chloroform in long, pale yellow, prismatic needles, m. p. 188° (yield, 8 g.; 98·4%) (Found: C, 35·7; H, 2·8; 8·459 mg. gave 14·785 mg. of AgCl + AgBr. $C_8H_7OCl_2Br$ requires C, 35·55; H, 2·6%; AgCl + AgBr, 14·822 mg.).

5-*Bromo*-m-2-*xylenol*.—Bromine (99·4 g.; 1 mol.) and *m*-2-xylenol (75 g.; 1 mol.) in acetic acid (575 c.c.) at 15° gave the bromo-xylenol, which crystallised from light petroleum in long, fine, colourless needles, m. p. 80—81° (Auwers and Markovitz record m. p. 79·5°) (yield, 118·5 g.; 95·9%).

4 : 5-*Dibromo*-m-2-*xylenol*.—Bromine (9 g.; 1·1 mols.) in dry chloroform (20 c.c.) was added quickly to a solution of 5-bromo-*m*-2-xylenol (10 g.; 1 mol.) in chloroform (100 c.c.) and a little aluminium bromide, and the mixture kept at 55° for 30 minutes. After being left overnight at room temperature, the solvent was removed; the residue crystallised from light petroleum in fine, colourless needles, m. p. 86° (yield, 13·2 g.; 94·8%), stable in alcohol solution to sulphur dioxide.

4 : 5 : 6-*Tribromo*-m-2-*xylenol*.—(*a*) Molten *m*-2-xylenol (18·3 g.; 1 mol.) was added to liquid bromine (144 g.; 6 mols.) at 0°, and after 2 hours excess of bromine was removed on the water-bath and the residue extracted with boiling 15% aqueous sodium hydroxide. The tribromo-compound crystallised from chloroform in pink-tinged needles, m. p. 206—207° (Auwers and Markovitz record m. p. 201°) (yield, 49·5 g.; 92·1%) (Found: C, 27·6; H, 2·4; Br, 67·5. Calc. for $C_8H_7OBr_3$: C, 26·7; H, 1·95; Br, 66·85%), stable to sulphur dioxide in alcohol and to boiling aqueous methyl-alcoholic silver nitrate. The use of excess of bromine in acetic acid gives only the 4 : 5-dibromo-derivative.

(*b*) Molten 4 : 5-dibromo-*m*-2-xylenol (2·5 g.; 1 mol.) and liquid bromine (2 g.; 2 mols.) at 0° for 12 hours gave the tribromo-derivative (yield, 2·9 g.; 90·5%).

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53. *Preparation of Certain Nuclear-substituted 2-Aminophenolsulphonic Acids.*

By W. F. Beech.

Methods for the preparation of some new 2-aminophenolsulphonic acid derivatives are described. The structures of these substances have been established.

The sulphonic acids of 2-aminophenol and its nuclear-substituted derivatives are of considerable importance on account of their wide use as diazo-components in the preparation of metallisable azo-dyes. During a systematic investigation of the technical properties of such dyes, certain 2-aminophenolsulphonic acid derivatives not previously described were prepared. The structures of these substances were established by orientation experiments.

A new dichloro-2-aminophenol-6-sulphonic acid was obtained from the nitration product of 5-chlorobenzoxazolone-7-sulphonic acid. According to the literature (Meister, Lucius & Brüning, D.R.-P. 197,807), the 6-nitro-derivative is formed, but the evidence given in support of this statement is not very satisfactory. It is known, however, that many benzoxazolone derivatives yield 6-nitrobenzoxazolones by direct nitration and this was found to be the case in the present instance (see below). The nitro-compound, 5-chloro-6-nitrobenzoxazolone-7-sulphonic acid (I; R = Cl, R′ = NO_2) was readily reduced to *5-chloro-6-aminobenzoxazolone-7-sulphonic acid* (I; R = Cl, R′ = NH_2) by iron and hydrochloric acid; the amine yielded 5 : 6-dichlorobenzoxazolone-7-sulphonic acid (I; R = R′ = Cl) (*sodium* salt) by diazotisation and the Sandmeyer reaction. Hydrolysis of this acid with aqueous sodium hydroxide gave 4 : 5-*dichloro*-2-*aminophenol*-6-*sulphonic acid* (II; R = R′ = Cl) which was converted into a sparingly soluble diazo-oxide by the action of nitrous acid. The diazo-oxide was decomposed by ethanol in the presence of cuprous oxide, 3 : 4-dichlorophenol-2-sulphonic acid (III; R = H, R′ = OH) being obtained (*sodium* salt). The potassium salt of the latter gave the known 2 : 3 : 4-trichlorophenol (Groves, Turner, and Sharp, *J.*, 1929, 522) on distillation with phosphorus pentachloride, a result which confirmed the structures assigned to the compounds described above.

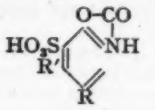
On methylation and subsequent treatment with phosphorus pentachloride in the cold, 3 : 4-dichlorophenol-2-sulphonic acid gave 3 : 4-*dichloroanisole*-2-*sulphonyl chloride* (III; R = Me, R′ = Cl); the latter was converted into a crystalline *ethylanilide* (III; R = Me, R′ = NEtPh) by treatment with ethylaniline.

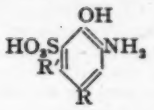
By sulphonation of 3 : 4-dichlorophenol, a dichlorophenolsulphonic acid differing from the 3 : 4-dichlorophenol-2-sulphonic acid described above was obtained. The *dichloroanisole-sulphonethylanilide* obtained from this substance, although it melted at approximately the same temperature as 3 : 4-dichloroanisole-2-sulphonethylanilide, depressed the m. p. of the latter. On prolonged heating with phosphorus pentachloride, the *potassium* salt of the dichlorophenolsulphonic acid yielded 1 : 2 : 4 : 5-tetrachlorobenzene, from which it follows that the substance was 4 : 5-dichlorophenol-2-sulphonic acid (IV; R = H, R′ = OH, R″ = H). On nitration the latter gave 3 : 4-dichloro-2-nitrophenol-6-sulphonic acid (IV; R = H, R′ = OH, R″ = NO_2) (*sodium* salt) which was reduced to 3 : 4-*dichloro*-2-*aminophenol*-6-*sulphonic acid* (IV; R = H, R′ = OH, R″ = NH_2) by iron and hydrochloric acid. By diazotisation followed by the Sandmeyer reaction, the aminophenolsulphonic acid yielded 2 : 3 : 4-trichlorophenol-6-sulphonic acid (*sodium* salt), the latter being readily converted into the known 2 : 3 : 4-trichlorophenol (*loc. cit.*) by boiling with concentrated hydrochloric or 10N-sulphuric acid.

By reactions similar to those employed for the preparation of 4 : 5-dichloro-2-aminophenol-6-sulphonic acid, 6-nitro-5-methylbenzoxazolone-7-sulphonic acid (I; R = Me, R′ = NO_2) (D.R.-P. 197,807) yielded successively 6-amino- and 6-chloro-5-methylbenzoxazolone-7-sulphonic acid (I; R = Me, R′ = Cl), the latter substance being hydrolysed to 2-*chloro*-5-*amino*-p-*cresol*-3-*sulphonic acid* (II; R = Me, R′ = Cl) by aqueous sodium hydroxide.

The sulphonation of *5-methoxybenzoxazolone* (V; R = H) with 20% oleum at 100° yielded the 6-sulphonic acid (V; R = SO_3H), as expected. This acid gave 2-*amino*-4-*methoxyphenol*-5-*sulphonic acid* (VI; R = H, R′ = SO_3H) on hydrolysis with sodium hydroxide, the structure of the latter being demonstrated by converting it into 4-*chloro*-2 : 5-*dimethoxybenzenesulphonethylanilide* by diazotisation and Sandmeyer reaction, followed by methylation and subsequent treatment of the 4-chloro-2 : 5-dimethoxybenzenesulphonic acid (*sodium* salt) thus formed with phosphorus pentachloride, the corresponding sulphonyl chloride being obtained. Treatment of the latter with ethylaniline yielded the ethylanilide. An authentic sample of 4-chloro-

2 : 5-dimethoxybenzenesulphonic acid was obtained from 4-chloro-2 : 5-dimethoxyaniline (Gen. Aniline, U.S.P. 1,919,580) by diazotising the latter, treating the diazo-solution with


(I.)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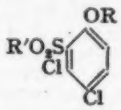
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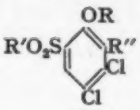
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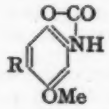
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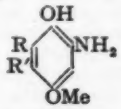
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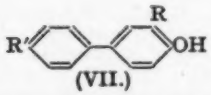
(VII.)

potassium ethyl xanthate (Leuckart, *J. pr. Chem.*, 1890, **41**, 179), and oxidising the product with potassium permanganate. The structure of 4-chloro-2 : 5-dimethoxyaniline does not appear to have been demonstrated with certainty. The substance is obtained from nitro-2 : 5-dimethoxyaniline (*loc. cit.*), which may be prepared either by nitration of 2 : 5-dimethoxyacetanilide and subsequent hydrolysis (Baessler, *Ber.*, 1884, **17**, 2121) or from nitro-4-chloro-2-anisidine by heating with potassium hydroxide and methanol (Badische Anilin- und Soda-Fabrik, D.R.-P. 141,975). It has been found, however, that nitro-2 : 5-dimethoxyaniline gives on reduction a diamine which does not condense with phenanthraquinone; hence, the substance is either 3- or 4-nitro-2 : 5-dimethoxyaniline. Since the chlorine atom of the nitro-4-chloro-2-anisidine is labile, the substance to which it gives rise on heating with potassium hydroxide and methanol is either 4- or 6-nitro-2 : 5-dimethoxyaniline. As the products of the two methods of synthesis are identical (D.R.-P. 141,975) the substance is 4-nitro-2 : 5-dimethoxyaniline.

In the hope of obtaining 2-amino-4-methoxyphenol-6-sulphonic acid (VI; R = SO_3H, R′ = H), 2-amino-4-methoxyphenol was sulphonated with 20% oleum, but the product was found to consist almost entirely of 2-amino-4-methoxyphenol-5-sulphonic acid. Chromatographic analysis of the dye obtained from the crude sulphonation product by diazotisation and coupling with β-naphthol indicated the presence of two coloured substances, one identical with that obtained in a similar manner from 2-amino-4-methoxyphenol-5-sulphonic acid prepared from 5-methoxybenzoxazolone: the second was present in small amount only. A similar analysis with the corresponding dye made from the purified sulphonation product showed the presence of one substance only, the major constituent of the first analysis. That the purified sulphonation product was identical with 2-amino-4-methoxyphenol-5-sulphonic acid prepared from 5-methoxybenzoxazolone was further demonstrated by converting each into 4-chloro-2 : 5-dimethoxybenzenesulphonethylanilide.

By sulphonating 3-nitro-4-hydroxydiphenyl (VII; R = NO_2, R′ = H) with concentrated sulphuric acid at 80° and reducing the product with iron and hydrochloric acid, an amino-hydroxydiphenylsulphonic acid was obtained which may be regarded as a 2-aminophenol derivative bearing a substituent phenyl group. The position of the sulphonic acid group was determined by deaminating the substance and subsequently fusing the *sodium* salt of the product with sodium hydroxide, the product being identified as 4 : 4′-dihydroxydiphenyl. This result establishes the structure of the aminohydroxydiphenylsulphonic acid as *3-amino-4-hydroxydiphenyl-4′-sulphonic acid* (VII; R = NH_2, R′ = SO_3H) and that of the nitro-compound as 3-nitro-4-hydroxydiphenyl-4′-sulphonic acid (VII, R = NO_2, R′ = SO_3H).

Experimental.

(Analyses by Mr. E. S. Morton. M. ps. are uncorrected.)

4 : 5-*Dichlorophenol-2-sulphonic Acid.*—3 : 4-Dichlorophenol (163 g.) was melted (m. p. 68°) and sulphuric acid monohydrate (65 c.c.) added rapidly with shaking. After 10 minutes the temperature rose spontaneously to 105°, crystals of the sulphonic acid separating. The reaction was completed by heating at 95—100° for 2 hours; the product was then dissolved in water (250 c.c.). Potassium chloride (70 g.) was added, and the product removed by filtration. *Potassium* 4 : 5-*dichlorophenol-2-sulphonate* was obtained by dissolving the latter in water and neutralising the resulting solution with potassium carbonate; it was purified by recrystallisation from hot water (Found : S, 11·4; K, 13·5. $C_6H_2O_4Cl_2SK$ requires S, 11·4; K, 13·9%).

Reaction of the potassium salt with phosphorus pentachloride. The dry potassium salt (40 g.) was mixed with phosphorus pentachloride (80 g.) and phosphoryl chloride (5 c.c.). The mixture was boiled gently under reflux for 8 hours and then distilled. The distillate was treated with water (350 c.c.) to

decompose phosphorus pentachloride and phosphoryl chloride, and the solid residue isolated. The latter was washed with N-sodium hydroxide (50 c.c.) and water (50 c.c.) and dried. The product (5 g.) was purified by crystallisation from β-ethoxyethanol and then from benzene until the m. p. became constant (140°) (Found: Cl, 65·2. Calc. for $C_6H_2Cl_4$: Cl, 65·75%). The m. p. was not depressed by admixture with an authentic sample of 1 : 2 : 4 : 5-tetrachlorobenzene.

4 : 5-*Dichloroanisole-2-sulphonamide.*—4 : 5-Dichlorophenol-2-sulphonic acid (potassium salt, 14·1 g.) was dissolved in water (50 c.c.), and the solution treated with 10N-sodium hydroxide (7 c.c.) and methyl sulphate (6 c.c.) at 30°, the reaction being completed by heating to 100°. The solution was then made just acid to Congo-red by addition of hydrochloric acid and evaporated by dryness. The residue was treated with phosphorus pentachloride (15 g.), and the resulting 4 : 5-dichloroanisole-2-sulphonyl chloride converted into 4 : 5-*dichloroanisole-2-sulphonamide* by treatment with excess of ammonia. The sulphonamide was purified by crystallisation from methanol; white needles, m. p. 206° (Found: N, 6·0; Cl, 27·9. $C_7H_7O_3NCl_2S$ requires N, 5·45; Cl, 27·75%).

4 : 5-*Dichloroanisole-2-sulphonethylanilide* was obtained by treating 4 : 5-dichloroanisole-2-sulphonyl chloride with excess of ethylaniline. It crystallised from methanol in white needles, m. p. 118° (Found: N, 3·95; Cl, 19·45. $C_{15}H_{15}O_3NCl_2S$ requires N, 3·9; Cl, 19·7%).

3 : 4-*Dichloro-2-nitrophenol-6-sulphonic Acid.*—3 : 4-Dichlorophenol (163 g.) was sulphonated as described above. The product was dissolved in water (250 c.c.), and the solution treated with nitric acid (72 c.c.. *d* 1·4) at 5°. After 10—15 minutes, a vigorous reaction started, the temperature rising to 55—60°. After being stirred at 55° for 5 minutes, the solution was cooled to 25°, and sodium chloride (70 g.) added. The *sodium* salt of 3 : 4-dichloro-2-nitrophenol-6-sulphonic acid separated as a yellow precipitate; it crystallised from water in yellow needles (Found: N, 4·45. $C_6H_2O_6NCl_2SNa$ requires N, 4·5%). For the next stage, the substance was not recrystallised; the total yield was dissolved in hot water (1 l.), and the solution decanted from a slight insoluble residue.

3 : 4-Dichloro-2-aminophenol-6-sulphonic acid was obtained by adding the hot solution of 3 : 4-dichloro-2-nitrophenol-6-sulphonic acid to a mixture of iron filings (300 g.), water (400 c.c.), and 10N-hydrochloric acid (8 c.c.) at 95—100°, the reaction mixture being subsequently maintained at 95—100° for 1 hour with mechanical stirring. The acid was isolated by rendering the reaction mixture alkaline towards litmus with sodium carbonate, filtering it whilst hot, and acidifying the filtrate with hydrochloric acid. It was purified by boiling the solution of the crude product in dilute sodium carbonate with carbon, filtering, and acidifying. Further purification was effected by crystallisation from hot water, from which the *hemihydrate* separated in the form of white needles (Found: C, 26·8; H, 2·35; N, 5·5; Cl, 26·25; S, 12·05. $C_6H_5O_4NCl_2S,\frac{1}{2}H_2O$ requires C, 26·95; H, 2·25; N, 5·25; Cl, 26·6; S, 12·0%).

2 : 3 : 4-*Trichlorophenol-6-sulphonic Acid.*—3 : 4-Dichloro-2-aminophenol-6-sulphonic acid (26·7 g.), dissolved in a solution of sodium hydroxide (4 g.) in water (150 c.c.), was diazotised at 5—10° by addition of sodium nitrite (7 g.) in water (10 c.c.), followed by 10N-hydrochloric acid (35 c.c.). The diazo-suspension was added to a solution of cuprous chloride (12 g.) in hydrochloric acid (100 c.c., *d* 1·18) at 30°, and the solution heated gradually to 100°. On cooling, the *sodium* salt of 2 : 3 : 4-trichlorophenol-6-sulphonic acid separated; it was purified by crystallisation from methanol (Found: Cl, 36·2; S, 10·7; Na, 7·6. $C_6H_2O_4Cl_3SNa$ requires Cl, 35·55; S, 10·7; Na, 7·7%). On boiling the substance with concentrated hydrochloric or 10N-sulphuric acid for several hours, 2 : 3 : 4-trichlorophenol, m. p. 80°, was obtained (Found: Cl, 53·15. Calc. for $C_6H_3OCl_3$: Cl, 53·95%). The benzoate melted at 142° (Holleman, *Rec. Trav. chim.*, 1920, **39**, 743, gives m. p. 141°).

5-*Chloro-6-aminobenzoxazolone-7-sulphonic Acid.*—5-Chloro-6-nitrobenzoxazolone-7-sulphonic acid (D.R.-P. 197,807) (potassium salt, 332 g.) was added cautiously to a mixture of iron filings (300 g.), water (600 c.c.), and 10N-hydrochloric acid (12 c.c.) at 95°; the reaction mixture was subsequently kept at this temperature for 1 hour and then made alkaline by addition of sodium carbonate. After filtering at the boil, the filtrate was made just acid to Congo-red with hydrochloric acid. For the next stage it was not necessary to isolate 5-*chloro-6-aminobenzoxazolone-7-sulphonic acid*, which is diazotised *in situ*. The substance is easily isolated if required by addition of concentrated hydrochloric acid to the solution (Found: N, 10·8. $C_7H_3O_5N_2ClS$ requires N, 10·6%).

5 : 6-*Dichlorobenzoxazolone-7-sulphonic Acid.*—The solution of 5-chloro-6-aminobenzoxazolone-7-sulphonic acid (total liquor) was diazotised at 0—5° by adding 10N-hydrochloric acid (250 c.c.), followed by sodium nitrite (60 g.) in water (100 c.c.). The diazo-suspension was decomposed by adding it to a solution of cuprous chloride (120 g.) in hydrochloric acid (400 c.c., *d* 1·18) at 30° and subsequently heating to 100°. On concentrating the solution and cooling, 5 : 6-dichlorobenzoxazolone-7-sulphonic acid crystallised out as the *sodium* salt; it was purified by crystallisation from hot water; white needles (Found: N, 4·7; Cl, 22·5; Na, 8·0. $C_7H_2O_5NCl_2SNa$ requires N, 4·6; Cl, 23·2; Na, 7·5%).

4 : 5-*Dichloro-2-aminophenol-6-sulphonic Acid.*—5 : 6-Dichlorobenzoxazolone-7-sulphonic acid (200 g.) was dissolved in hot water (1200 c.c.), and 10N-sodium hydroxide (300 c.c.) added. The solution was kept at 95—100° for 3 hours, neutralised with concentrated hydrochloric acid, concentrated to 750 c.c. and then made strongly acid with hydrochloric acid. The crude 4 : 5-*dichloro-2-aminophenol-6-sulphonic acid* which separated was purified similarly to its 3 : 4-dichloro-analogue (yield, 130 g.). It crystallised from water in white needles (Found: C, 28·0; H, 2·1; N, 5·05; Cl, 27·9; S, 12·25. $C_6H_5O_4NCl_2S$ requires C, 27·9; H, 1·95; N, 5·45; Cl, 27·5; S, 12·4%).

3 : 4-*Dichlorophenol-2-sulphonic Acid.*—4 : 5-Dichloro-2-aminophenol-6-sulphonic acid (43 g.) was dissolved in sodium hydroxide (7 g.) in water (100 c.c.), and a solution of sodium nitrite (12 g.) in water (20 c.c.) added. Diazotisation was effected at 10° by adding 10N-sulphuric acid (85 c.c.) rapidly. The diazo-oxide was filtered off, washed with ethanol (25 c.c.), and suspended in ethanol (500 c.c.). Cuprous oxide (20 g.) was then added, and after the vigorous reaction had subsided, the reaction mixture was boiled under reflux for 3 hours. The ethanol was removed, and the residue extracted with dilute potassium carbonate solution (200 c.c.) at the boil. The solution was filtered, and the filtrate treated with a small quantity of sodium hyposulphite (dithionite), after which the product was isolated by saturating the solution with potassium chloride and cooling to 20°. 3 : 4-Dichlorophenol-2-sulphonic

acid separated as the *potassium* salt, which was purified by crystallisation from hot water; white needles (Found: Cl, 25·4; K, 13·75. $C_8H_3O_4Cl_2SK$ requires Cl, 25·25; K, 13·9%).

3 : 4-*Dichloroanisole-2-sulphonethylanilide* was prepared from 3 : 4-dichlorophenol-2-sulphonic acid by the method described for the isomeric 4 : 5-dichloro-compound; white plates from methanol, m. p. 117° (Found: C, 49·95; H, 4·3; N, 3·75; Cl, 20·15. $C_{15}H_{15}O_3NCl_2S$ requires C, 50·0; H, 4·15; N, 3·9; Cl, 19·7%). The m. p. was depressed on admixture with the isomeric 4 : 5-dichloro-compound.

Reaction of the Potassium Salt of 3 : 4-*Dichlorophenol-2-sulphonic Acid with Phosphorus Pentachloride.*—The reaction and subsequent distillation were performed in the manner described for the 4 : 5-dichloro-analogue. The greater part of the product was soluble in N-sodium hydroxide, from which it was reprecipitated by hydrochloric acid. The substance was purified by steam distillation and subsequent crystallisation from ligroin; white needles, m. p. 80° (Found: Cl, 53·4. Calc. for $C_6H_3OCl_3$: Cl, 53·95%). The benzoate melted at 142° (Holleman, *Rec. Trav. chim.*, 1920, **39**, 743, gives m. p. 141°).

2-*Chloro*-5-*amino*-p-*cresol*-3-*sulphonic acid* was prepared from 6-nitro-5-methylbenzoxazolone-7-sulphonic acid (D.R.-P. 197,807) (potassium salt, 312 g.) *via* the corresponding 6-amino- and 6-chloro-acids, the method being the same as for 4 : 5-dichloro-2-aminophenol-6-sulphonic acid. The required acid (110 g.) was purified similarly to 3 : 4-dichloro-2-aminophenol-6-sulphonic acid. It crystallised from water in white needles (Found: C, 35·55; H, 3·8; N, 5·7; S, 13·0; Cl, 15·25. $C_7H_8O_4NClS$ requires C, 35·4; H, 3·4; N, 5·9; S, 13·5; Cl, 14·95%).

2-Nitro-4-methoxyphenol was obtained by boiling technical 3-nitro-*p*-anisidine (168 g.) under reflux with potassium hydroxide (130 g.) in water (1500 c.c.) for 16 hours with stirring. The product was isolated by acidification and cooling. The crude product (155 g., m. p. 80°) was sufficiently pure for the next stage. A small sample, recrystallised from ethanol, melted at 82° (Robinson and Smith, *J.*, 1926, 393, give m. p. 79—80°). Reduction of this in alkaline solution with sodium hyposulphite (dithionite) and addition of sulphuric acid precipitated first 2-amino-4-methoxyphenol as plates which darkened rapidly in air, and then the sulphate, which was dried at 50°.

5-*Methoxybenzoxazolone* was obtained by treating a concentrated, aqueous alkaline solution of 2-amino-4-methoxyphenol with carbonyl chloride at 10—20°, maintaining faint alkalinity until diazotisable material disappeared. On acidifying the solution with 10N-sulphuric acid, the oxazolone separated; it crystallised from hot water in white needles, m. p. 170° (Found: C, 57·95; H, 4·35; N, 8·65 $C_8H_7O_3N$ requires C, 58·2; H, 4·25; N, 8·5%).

5-*Methoxybenzoxazolone-6-sulphonic Acid.*—5-Methoxybenzoxazolone (50 g.) was added to 20% oleum (125 c.c.), the temperature being kept below 50°. The solution was then heated at 95—100° for 2 hours, cooled to 10°, and poured on ice (400 g.). Sodium chloride (120 g.) was added, and the solution stirred for 24 hours. The product was filtered off and washed with brine.

2-*Amino-4-methoxyphenol-5-sulphonic Acid.*—The total yield of the foregoing acid was dissolved in hot water (500 c.c.), and sodium hydroxide (40 g.) added. The solution was kept at 95—100° for 3 hours, made acid to Congo-red with hydrochloric acid and concentrated to 150 c.c. The solution was then made strongly acid with hydrochloric acid and cooled to 10°. Crude 2-*amino-4-methoxyphenol-5-sulphonic acid* (35 g.) separated; it was purified in a similar manner to 3 : 4-dichloro-2-aminophenol-6-sulphonic acid; white needles, turning dark in air (Found: C, 35·65; H, 4·55; N, 6·05. $C_7H_9O_5NS,H_2O$ requires C, 35·45; H, 4·65; N, 5·9%).

Direct Sulphonation of 2-*Amino-4-methoxyphenol.*—The sulphate of 2-amino-4-methoxyphenol (200 g.) was added to 20% oleum (500 c.c.), the temperature being kept below 50°. The solution was heated at 60° for 1 hour and then poured on ice. The product was filtered off and dissolved in dilute sodium carbonate solution (750 c.c.). The solution was decolorised (carbon), filtered, and acidified with hydrochloric acid. The product, consisting mainly of the above 5-sulphonic acid (130 g.), was purified by crystallisation from hot water (Found: N, 5·9; OCH_3, 12·8. $C_7H_9O_5NS,H_2O$ requires N, 5·9; OCH_3, 13·1%).

4-*Chloro*-2 : 5-*dimethoxybenzenesulphonic Acid.*—(a) 2-Amino-4-methoxyphenol-5-sulphonic acid (23·7 g.), dissolved in N-sodium hydroxide (100 c.c.), was diazotised at 10° by addition of sodium nitrite (7 g.) followed by 10N-hydrochloric acid (35 c.c.). The diazo-suspension was added to cuprous chloride (11 g.) in hydrochloric acid (70 c.c., *d* 1·18) at 40°, the solution being subsequently raised to the boil. After precipitation of copper salts with hydrogen sulphide and filtering, the filtrate was evaporated to dryness. The residue was dissolved in water (75 c.c.), and the solution made faintly alkaline with sodium carbonate. Methylation was effected by adding sodium hydroxide (5 g.) followed by methyl sulphate (12 c.c.) to the solution at 25° and subsequently heating to 70°. *Sodium 4-chloro*-2 : 5-*dimethoxybenzenesulphonate* was isolated from the solution by saturating the latter with sodium chloride and cooling to 20°. It crystallised from water in white needles (Found: C, 35·3; H, 3·3; Cl, 12·55; Na, 8·05. $C_8H_8O_5ClSNa$ requires C, 34·95; H, 2·9; Cl, 12·9; Na, 8·4%) and was characterised by conversion into the amide and the ethylanilide.

(b) 4-Chloro-2 : 5-dimethoxyaniline (18·8 g.), dissolved in water (100 c.c.) and 10N-hydrochloric acid (25 c.c.), was diazotised at 0° by addition of a solution of sodium nitrite (6·9 g.) in water (10 c.c.). The diazo-solution was added gradually to a solution of potassium ethyl xanthate (16 g.) in water (100 c.c.) cooled in ice. When addition was complete, the resulting suspension was heated slowly to 90°. The oily substance which separated was removed and dissolved in acetone (200 c.c.). Oxidation was effected by adding a saturated aqueous solution of potassium permanganate at the boil until a slight excess of the latter remained. The solution was then filtered, and the filtrate evaporated to dryness. The product crystallised from water in white needles.

The sulphonic acid (sodium salt, 27·5 g.) was mixed with phosphorus pentachloride (23 g.), the reaction being completed by heating to 95° for 10 minutes. After being stirred with ice, the sulphonyl chloride was filtered off and washed with cold water. Treatment of this with excess of ammonia solution, and crystallisation from methanol afforded the *amide* in white needles, m. p. 207° (Found: C, 38·15; H, 4·2; N, 5·7; $C_8H_{10}O_4NClS$ requires C, 38·15; H, 4·0; N, 5·55%), and the *sulphonethylanilide* was similarly obtained by use of excess of ethylaniline in 50% aqueous alcohol, crystallising from methanol

in large white needles, m. p. 114° (Found : C, 54·5; H, 4·9; N, 4·3. $C_{16}H_{15}O_4NClS$ requires C, 54·0; H, 5·05; N, 3·95%).

The sulphonamide and sulphonethylanilide obtained from 4-chloro-2 : 5-dimethoxybenzenesulphonic acid prepared by method (b) were considered authentic samples, and their m. ps. were not depressed by admixture with similar derivatives obtained from the acid prepared by method (a), this result being obtained irrespective of whether the starting material of (a) was prepared by direct sulphonation of 2-amino-4-methoxyphenol or by hydrolysis of 5-methoxybenzoxazolone-6-sulphonic acid.

3-Nitro-4-hydroxydiphenyl-4′-sulphonic Acid.—3-Nitro-4-hydroxydiphenyl (Raiford and Colbert, *J. Amer. Chem. Soc.*, 1925, **47**, 1454) (86 g.) was added to sulphuric acid (234 c.c. *d* 1·84) at 20°. The temperature was then raised to 80° during 10 minutes, after which the solution was poured on ice. The resulting suspension was diluted with sufficient water to give a clear solution at 50°. The latter was saturated with sodium chloride, cooled to 15°, and the resulting 3-nitro-4-hydroxydiphenyl-4′-sulphonic acid (100 g.) collected.

3-Amino-4-hydroxydiphenyl-4′-sulphonic Acid.—The foregoing acid (100 g.) was added to a mixture of iron filings (100 g.), water (400 c.c.), and 10N-hydrochloric acid (8 c.c.) at 95°. The reaction mixture was kept at 95—100° with stirring for 2 hours, and then made alkaline with sodium hydroxide and filtered whilst hot. The filtrate was acidified with concentrated hydrochloric acid and cooled to 20°, crude *3-amino-4-hydroxydiphenyl-4′-sulphonic acid* (80 g.) separating. The substance was purified in a similar manner to 3 : 4-dichloro-2-aminophenol-6-sulphonic acid. It crystallised from water in white needles (Found : C, 50·95; H, 4·7; N, 5·15; S, 11·1. $C_{12}H_{11}O_4NS,H_2O$ requires C, 50·9; H, 4·6; N, 4·95; S, 11·3%).

4-Hydroxydiphenyl-4′-sulphonic Acid.—4-Amino-4-hydroxydiphenyl-4′-sulphonic acid (5·66 g.), dissolved in sodium hydroxide (2 g.) in water (35 c.c.), was diazotised at 5° by adding 2N-sodium nitrite (10 c.c.) followed by 10N-sulphuric acid (15 c.c.). The diazo-oxide was filtered off, washed with ethanol (10 c.c.), and suspended in ethanol (100 c.c.). After addition of cuprous oxide (5 g.), the suspension was raised to the boil during 15 minutes, and then boiled under reflux for 3 hours. The ethanol was removed, and the residue extracted with boiling dilute sodium carbonate solution (125 c.c.). The solution was filtered, and the filtrate treated with a small quantity of sodium hyposulphite (dithionite). *Sodium 4-hydroxydiphenyl-4′-sulphonate* separated on cooling; it was purified by crystallisation from hot water (Found : S, 9·5; Na, 7·0; H_2O, 12·3. $C_{12}H_9O_4SNa,2H_2O$ requires S, 10·4; Na, 7·45; H_2O, 11·7%).

4 : 4′-Dihydroxydiphenyl.—The foregoing sodium salt was fused with sodium hydroxide as described by Van Meter, Bianculli, and Lowy (*J. Amer. Chem. Soc.*, 1940, **62**, 3146). The product, after purification, melted at 270° (m. p. of 4 : 4′-dihydroxydiphenyl, 272°); it was characterised by conversion into the diacetyl derivative, m. p. and mixed m. p. 161° (Found : C, 70·5; H, 5·15. Calc. for $C_{16}H_{14}O_4$: C, 71·1; H, 5·2%).

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54. *Activity Coefficients of Zinc Iodide.*

By J. R. PARTINGTON and F. G. TORTO.

The electromotive force of the cell ZnHg(2 phases)|ZnI_2(*m*)|AgI–Ag, in the concentration range 0·007—0·400 molal, at 25° was measured. The standard potential was calculated as 0·61047 v. by an application of the Gronwall, La Mer, and Greiff extended-term equation. The activity coefficients calculated were found to be those of a typical strong electrolyte.

ACTIVITY coefficients of zinc iodide were obtained by Bates (*J. Amer. Chem. Soc.*, 1938, **60**, 2983) from measurements of the e.m.f. of the cell ZnHg(2 phases)|ZnI_2(*m*)|AgI–Ag, over the concentration range 0·005—0·800 molal, at 5° intervals from 5° to 40° inclusive. The activity coefficients obtained were those of a typical strong electrolyte, although at molalities above 0·2 they increased slightly with concentration, an effect which was attributed to increasing solubility of silver iodide in zinc iodide solutions. Further measurements were carried out by Baxter (M.Sc. Thesis, London University, 1939), and by Egan and Partington (*J.*, 1943, 157), who employed the cell Zn|ZnI_2 (*m*), Hg_2I_2(s)|Hg|Hg_2I_2 ZnI_2 (*m*)|Zn. The results they obtained were consistent with one another, and gave activity coefficients which, although normal below 0·05 molar (*i.e.*, agreeing with those obtained by Bates), increased rapidly with concentration above this concentration, reaching the abnormally high value of 2·082 at $c = 0·2631$. Stokes and Lieven (*J. Amer. Chem. Soc.*, 1946, **68**, 1582) and Stokes and Stokes (*Trans. Faraday Soc.*, 1945, **41**, 12) obtained activity coefficients by the isopiestic vapour pressure method, using potassium chloride as reference, over the concentration range 0·01—10 molar, and their activity coefficients were in good agreement with those of Bates. In this research, measurements of the e.m.f. of the cell ZnHg(2 phases)|ZnI_2 (*m*)|AgI–Ag have been made in the concentration range 0·007—0·400 molal.

Experimental.

Considerable difficulty was experienced in preparing and using the materials for the cells so as to obtain satisfactory results, and the essential experimental details finally adopted are therefore briefly set out below.

Zinc Iodide.—Constant-boiling hydriodic acid, prepared by passing hydrogen sulphide through a suspension of iodine in water, filtering, and distilling in the dark, was partly neutralised with pure zinc (99·996%, from the Imperial Smelting Co., Avonmouth) till the amber colour disappeared. Alternatively, the acid was neutralised with zinc oxide, and the solution decolourised by warming, in small quantities at a time, and with constant shaking, with a little precipitated silver. The colourless solution so obtained usually gave a slight precipitate with hydrochloric acid, but after standing for a week over zinc, this effect disappeared.

The stock solutions so prepared were kept under hydrogen which had been passed over red-hot copper. Weighed quantities of solution were analysed for zinc as pyrophosphate, and the cell solutions were made by diluting weighed quantities of stock solution with weighed quantities of boiled-out water which had been allowed to cool in an atmosphere of purified hydrogen.

Zinc Amalgam.—This was prepared by warming pure zinc (5 parts) and redistilled mercury (95 parts) in an atmosphere of hydrogen and washing with 0·001N-nitric acid and then with water, and was dried by passing dry hydrogen over the surface of the warm amalgam, which was kept under hydrogen.

Cohen (*Z. physikal. Chem.*, 1905, **34**, 612) gave the potential of the zinc amalgam electrode as 0·6 mv. with respect to pure zinc, but Spencer (*Z. Electrochem.*, 1905, **11**, 681) found it to be zero, or practically so, for amalgams more concentrated than 0·65%. Clayton and Vosburgh (*J. Amer. Chem. Soc.*, 1936, **58**, 2093) with the cell $Zn|Zn^{++}|ZnHg$, in which the solutions were zinc chloride, sulphate, or acetate, concluded that the potential of zinc amalgam was zero with respect to pure zinc. Their cell solutions were free from dissolved oxygen and the cells were filled in complete absence of air. That this is necessary for the reproducibility of this electrode was shown by Horsch (*ibid.*, 1919, **41**, 1787), with the cell $ZnHg(3{\cdot}6\%)|ZnSO_4,Hg_2SO_4|Hg$. Scatchard and Tefft (*ibid.*, 1930, **52**, 2272), with the cell $ZnHg|ZnCl_2,AgCl|Ag$, found a lowering of e.m.f. of 3—5 mv. on passing air over the surface of the amalgam, and this was accompanied by the formation of a dark scum on the surface.

Silver–Silver Iodide Electrodes.—These were made by heating a paste of silver iodide (1 part) and silver oxide (9 parts) on a platinum-wire spiral at 450—475° for 20 minutes in an electric furnace (Bates, *loc. cit.*). The electrodes were prepared shortly before use, and sets of two prepared at the same time and short-circuited in 0·04N-potassium iodide solution, from which oxygen had been removed by alternately evacuating and sweeping out with purified hydrogen, had an asymmetry potential of only 0·03 mv. To attain reproducibility of this order, rigid exclusion of dissolved oxygen from the solutions is necessary (cf. Owen, *J. Amer. Chem. Soc.*, 1935, **57**, 1527; Taylor and Smith, *Nat. Bur. Stand. J. Res.*, 1939, **22**, 307). It was therefore necessary to perform the operation of filling the cell in an atmosphere of hydrogen. The cell vessel, with the zinc amalgam and the silver–silver iodide electrode in place, was alternately evacuated and filled with hydrogen several times, and the air-free solution forced in by hydrogen pressure. The cell was placed in a thermostat at 25° (± 0·02°); the thermostat, and the potentiometer and its accessories stood on an equipotential metal-foil surface (White, *J. Amer. Chem. Soc.*, 1914, **36**, 2011).

Results.—Table I gives the e.m.f. for different solutions. Duplicate cells agreed to within 0·1 mv.; the cells usually reached equilibrium within ½ hour in the thermostat, but solutions below 0·01738m required a longer time. The e.m.f.s then remained constant for 6—8 hours, after which most cells showed a gradual increase. The values of e for $m = 0{\cdot}0080$ and 0·0085 were obtained by interpolation from a large-scale plot of e against log m. Cells containing solutions which had not been decolourised did not come to satisfactory equilibrium.

Table I.

Electromotive forces at 25°.

m (molality).	e (volts).	m (molality).	e (volts).	m (molality).	e (volts).	m (molality).	e (volts).
0·00695	0·7943	0·00901	0·7852	0·03442	0·7396	0·11475	0·6977
0·00750	0·7916	0·01222	0·7745	0·04620	0·7293	0·16340	0·6843
0·00800	0·7893	0·01738	0·7626	0·06944	0·7154	0·21993	0·6738
0·00850	0·7872	0·02433	0·7515	0·09021	0·7067	0·39060	0·6495

Discussion.

The e.m.f. is given by

$$e = e_0 - 2{\cdot}303 \,.\, 3RT \log (\gamma\, m_{\pm}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where γ is the mean stoicheiometric activity coefficient, and $m_{\pm}$ the mean molality:

$$m_{\pm} = m\,(\nu_+{}^{\nu_+}\nu_-{}^{\nu_-})^{1/\nu} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

ν_+ and ν_- being the numbers of positive and negative ions, respectively, formed by the ionisation of one molecule of electrolyte, and $\nu = \nu_+ + \nu_-$. In this case $m_{\pm} = m \times 4^{1/3}$. At 25°, (1) becomes

$$e = e_0 - 0{\cdot}08871 \log \gamma - 0{\cdot}08871 \log m - 0{\cdot}01782 \quad . \quad . \quad . \quad (3)$$

$$e + 0{\cdot}08871 \log m + 0{\cdot}01782 = e_0' = e_0 - 0{\cdot}08871 \log \gamma \quad . \quad . \quad (4)$$

where e_0 is the standard potential. The evaluation of the standard potential e_0 was carried out

by Gronwall, La Mer, and Greiff's extended form of the Debye–Hückel equation (*J. Physical Chem.*, 1931, **35**, 2245) which, with numerical constants substituted, is

$$-\log\gamma = 2\left[1{\cdot}5492\,\frac{1}{(10^8a)}\cdot\frac{x}{1+x} + 0{\cdot}22105\,\frac{1}{(10^8a)^2}\,\phi_1 - 0{\cdot}15771\,\frac{3}{(10^8a)^3}\,\phi_2 - 0{\cdot}15771\,\frac{9}{(10^8a)^3}\,\phi_3\right] \quad (5)$$

where $\phi_1 = 10^3[\frac{1}{2}X_2(x) - {}_1Y_2(x)]$, $\phi_2 = 10^3[\frac{1}{2}X_3^*(x) - 2Y_3^*(x)]$, $\phi_3 = 10^3[\frac{1}{2}X_3(x) - 2Y_3(x)]$, and $x = \kappa a$;

$1/\kappa$ and a are, respectively, the thickness of the ion atmosphere and the mean distance of closest ionic approach in the Debye–Hückel theory. The values of the natural constants used are $N = 6{\cdot}023 \times 10^{22}$ mole^{-1}, $k = 1{\cdot}3804 \times 10^{-16}$ erg-deg.$^{-1}$, $e = 4{\cdot}8025 \times 10^{10}$ e.s.u., $T_0 = 273{\cdot}16°$, and $D_{25} = 78{\cdot}54$, as quoted by Manov, Bates, Hamer, and Acree (*J. Amer. Chem. Soc.*, 1943, **65**, 1765).

The process for evaluating e_0 is similar to that used by Gronwall, La Mer, and Greiff, by La Mer and Cowperthwaite (*ibid.*, 1931, **53**, 4333), La Mer and Parks (*ibid.*, p. 2040), Bates (*ibid.*, 1939, **61**, 308), and Quentin (*Compt. rend.*, 1935, **200**, 1754). A likely value of a is assumed and $\log\gamma$ calculated for a series of molalities, with the values of ϕ_1 and ϕ_3 tabulated by La Mer, Gronwall, and Sandved (*Physikal. Z.*, 1929, **29**, 358), and of ϕ_2 tabulated by Gronwall, La Mer, and Greiff. The value of e_0 is then found from the relation

$$e = e_0 - 0{\cdot}08871\log\gamma \quad (6)$$

The value of a giving the most constant value of e_0 is taken as the likeliest value, and the corresponding value of e_0 is employed in finding $\log\gamma$ by equation (6).

TABLE II.

m.	$a = 5{\cdot}9$ Å.	$a = 6{\cdot}0$ Å.	$a = 6{\cdot}1$ Å.	$a = 6{\cdot}2$ Å.	$a = 6{\cdot}3$ Å.
0·00695	0·113253	0·114259	0·114212	0·113249	0·112748
0·00750	0·116862	0·117592	0·117081	0·116538	0·116050
0·00800	0·119740	0·120501	0·119967	0·119399	0·118883
0·00850	0·123364	0·123321	0·122726	0·122139	0·121598

TABLE III.

m.	$a = 5{\cdot}9$ Å.	$a = 6{\cdot}0$ Å.	$a = 6{\cdot}1$ Å.	$a = 6{\cdot}2$ Å.	$a = 6{\cdot}3$ Å.
0·00695	0·61064	0·61055	0·61055	0·61064	0·61069
0·00750	0·61056	0·61050	0·61047	0·61059	0·61063
0·00800	0·61048	0·61041	0·61046	0·61051	0·61055
0·00850	0·61038	0·61041	0·61038	0·61051	0·61056
Mean	0·61051	0·61047	0·61047	0·61056	0·61061
Total deviation from mean	0·00034	0·00023	0·00018	0·00021	0·00021

Table II gives the values of $-\log\gamma$ for a values of 5·9, 6·0, 6·1, 6·2, and 6·3 Å. Table III gives the values of e_0 obtained for these values of a, as well as the total deviations from the mean values of e_0. The final value of a was taken as 6·1 Å., this giving $e_0 = 0{\cdot}61047$ v. Stokes and Stokes (*loc. cit.*) repeated Bates's graphical extrapolation of e_0, with the revised constants and $a = 6$ Å., and obtained $e_0 = 0{\cdot}61040$ v.

The stoicheiometric activity coefficients were calculated by (6), and in Table IV are compared with those calculated by the Debye–Hückel equations

$$-\log\gamma = \frac{1{\cdot}0184\sqrt{I}}{1 + 0{\cdot}3286a\sqrt{I}} + \log(1 + 0{\cdot}054m) \quad (7)$$

and

$$-\log\gamma = \frac{1{\cdot}0184\sqrt{I}}{1 + 0{\cdot}3286a\sqrt{I}} + \log(1 + 0{\cdot}054m) - CI \quad (8)$$

where $I = \frac{1}{2}\Sigma m_i z_i^2$, and C is a constant. The most suitable value of C was found to be 0·115.

TABLE IV.

m.	E.m.f.	Eqn. (7).	Eqn. (8).	*m*.	E.m.f.	Eqn. (7).	Eqn. (8).
0·00695	0·767	0·769	—	0·03442	0·641	0·631	0·643
0·00750	0·762	0·763	—	0·04620	0·624	0·607	0·623
0·00800	0·759	0·758	—	0·06944	0·595	0·570	0·594
0·00850	0·752	0·753	—	0·09021	0·574	0·548	0·579
0·00901	0·749	0·748	—	0·11475	0·570	0·528	0·568
0·01222	0·729	0·722	0·726	0·16340	0·567	0·501	0·557
0·01738	0·699	0·692	0·698	0·21993	0·553	0·479	0·555
0·02433	0·666	0·662	0·670	0·39060	0·585	0·440	0·575

To obtain an idea of the magnitude of the second dissociation $ZnI^{+} \rightleftharpoons Zn^{++} + I'$, the method of Scatchard and Tefft (*J. Amer. Chem. Soc.*, 1930, **52**, 2270) as modified by Harned and Fitzgerald (*ibid.*, 1936, **58**, 2624) was used. On substituting the Debye–Hückel limiting expression with an added linear term, *viz.*, $-\log\gamma = h\sqrt{m} + Bm$, equation (3) gives

$$e_0' = e + 0{\cdot}08871 \log m + 0{\cdot}01782 - 0{\cdot}155\sqrt{m} = e_0 - Bm \quad . \quad . \quad . \quad (9)$$

Scatchard and Tefft showed that e_0' when plotted against $\sqrt{m}$ for various bivalent metal chlorides gave curves with a characteristic maximum, which they attributed to incomplete dissociation of the ion MX^{+}. To obtain an estimate of the corresponding equilibrium constant K_2 a plot of $e_0' - e_0$ against $m^{1/2}$ is compared with theoretical plots constructed for different values of K_2. The plot for the zinc iodide data obtained in this research corresponded with a very large value of K_2 in the dilute solutions. By the same method, Bates estimated K_2 as being of the order of 10, and Sillén and Liljeqvist (*Svensk Kem. Tidskr.*, 1944, **56**, 85), by potentiometric titration, obtained a value of about 5. It appears, therefore, that the assumption of complete dissociation of zinc iodide is justified, this salt behaving as a normal strong electrolyte. The activity coefficients obtained are in good agreement with those obtained by Bates, Stokes, and Stokes, and Stokes and Lieven. The value of 6·1 A. obtained for the mean distance of closest ionic approach is smaller than the minimum distance of 7 A. required by Bjerrum's theory (*Kgl. Danske Vidensk. Selskab.*, 1926, **7**, No. 9) to exclude ion association for a bi-univalent electrolyte, and hence a certain amount of ion association of this kind would have been expected to occur in zinc iodide solutions.

QUEEN MARY COLLEGE, MILE END ROAD, E. 1. [*Received, March 25th*, 1947.]

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55. *Lipoid-soluble Alloxazine Derivatives.*

By WALTER C. J. ROSS.

The preparation of a number of lipoid-soluble derivatives of alloxazine is described. The new compounds have no effect on tumour growth, but several cause pigmentation of the hair of the albino rat.

LETTRÉ and FERNHOLZ (*Ber.*, 1940, **73**, 436) have described the preparation of a number of lipoid-soluble derivatives of alloxazine and have tested them for carcinogenic activity. No such action was found during the period of their experiments, which they admitted were of a preliminary nature. They did, however, claim that one of their flavin derivatives—9-*n*-butyl-5 : 6-benz*iso*alloxazine—had a specific damaging effect on cancer cells *in vitro*. Haddow (unpublished results) has tested a number of the compounds described by Lettré and Fernholz for their action on the growth of the transplanted Walker rat carcinoma, but no inhibitory action has been found. The action of the 9-*n*-butyl derivative on tumour cells growing *in vitro* has also been tested by Ludford by a technique similar to that employed by Lettré and his co-workers, but again with negative results (unpublished work). In this paper we describe the preparation of further lipoid-soluble compounds related to alloxazine which have been made primarily in order to test their effect on tumour growth.

Two general methods have been employed for the synthesis of the alloxazines; the first involves the condensation of a substituted or unsubstituted *o*-diamine with alloxan, and the second makes use of the reaction between an *o*-diketone and a 4 : 5-diaminopyrimidine.

*9-Phenyl-7 : 8-benziso**alloxazine* (I) was obtained by condensation of alloxan with 2-amino-1-anilinonaphthalene. This diamine does not appear to have been made before by an unambiguous method. Harden (*Annalen*, 1889, **255**, 161) claimed to have obtained it by the action of phenylhydrazine on 1-nitroso-2-naphthylamine, but when Morgan and Godden (*J.*,

1910, **97**, 1721) attempted to repeat this work they obtained a product which did not have properties corresponding to the phenyldiamine. Noelting, Grandmougin, and Freimann (*Ber.*, 1909, **42**, 1381) considered that they had isolated this substance from the reduction products of *O*-alkyl derivatives of 2-benzeneazo-1-naphthol. The properties of the compound, which has now been obtained by the method outlined below, agree well with those of the substance described by Noelting *et al.* and so there is little doubt that these workers were the first to obtain 2-amino-1-anilinonaphthalene. The nitration of α-naphthylamine acetate followed by hydrolysis of the product gives a mixture from which 2-nitro-1-naphthylamine can be isolated by the method of Hodgson and Walker (*J.*, 1933, 1205). When the nitro-amine thus obtained is heated with bromobenzene in the presence of potassium carbonate and cuprous iodide, 2-nitro-1-anilinonaphthalene is formed; this is identical with a compound previously prepared by the action of aniline on 1 : 2-dinitronaphthalene (Vesely and Dvorak, *Bull. Soc. chim.*, 1923, **33**, 319). Reduction of the product with stannous chloride affords 2-amino-1-anilinonaphthalene. It was observed that 9-phenyl-7 : 8-benz*iso*alloxazine and other alloxazines now described tenaciously retain solvents after crystallisation, and it is only after intensive drying at high temperature or in some cases after sublimation in a high vacuum that satisfactory analytical figures can be obtained. Most of the new alloxazines have no true m. p. but decompose with evolution of gas at temperatures which are to some extent dependent on the rate of heating.

3 : 4-Diaminodiphenyl (obtained by the improved method of Bell and Kenyon, *J.*, 1926, 2705) condenses with alloxan to give 6- or 7-*phenylalloxazine* (II, *a* or *b*). 3-Nitro-4-aminodiphenyl (Fichter and Sulzberger, *Ber.*, 1904, **37**, 881) affords 3-*nitro*-4-*anilinodiphenyl* when heated with bromobenzene, potassium carbonate, and cuprous iodide, and the oily reduction product of this nitro-amine readily reacts with alloxan giving 6 : 9-*diphenyl*iso*alloxazine* (III). 3-*Nitro*-4-(1′-*naphthylamino*)*diphenyl* was obtained by heating the corresponding nitro-amine with α-bromonaphthalene in the presence of potassium and copper acetates. Catalytic reduction of the nitro-group gave 3-*amino*-4-(1′-*naphthylamino*)*diphenyl*, which did not react with alloxan under the usual conditions.

2 : 3-Diaminonaphthalene condenses with alloxan in dilute hydrochloric acid solution with the production of 6 : 7-*benzalloxazine* (IV). The compound can be obtained in the form of deep red crystals when sublimed in a high vacuum; it is the most deeply coloured alloxazine of the present series.

Waldman and Beck (*Annalen*, 1940, **545**, 52) have prepared 1-(2′-nitroanilino)naphthalene by heating *o*-bromonitrobenzene with α-naphthylamine in the presence of sodium acetate, and the same product has now been obtained by the action of α-bromonaphthalene on *o*-nitroaniline. They reduced this compound with sodium sulphide in ether or with stannous chloride in ethanolic hydrochloric acid; it is now found that 1-(2′-aminoanilino)naphthalene can be more conveniently prepared by catalytic reduction using Raney nickel. The diamine can be converted into 9-(1′-*naphthyl*)iso*alloxazine* (V) in the usual way. 2-(2′-Nitroanilino)naphthalene has been obtained by Warren and Smiles (*J.*, 1932, 2774) by heating 2-*o*-nitroanilinonaphthyl-1-sulphinic acid with acetic acid or by the reduction of either 2-*o*-nitroanilino-1-naphthyl disulphide or bis-2-*o*-nitroanilino-1-naphthyl sulphoxide with hydriodic acid. It has now been prepared by the more straightforward method of heating *o*-nitroaniline with β-bromonaphthalene in the presence of potassium carbonate and cuprous iodide. Catalytic reduction of the nitroamine affords 2-(2′-*aminoanilino*)*naphthalene* which condenses with alloxan to give 9-(2′-*naphthyl*)iso*alloxazine* (VI).

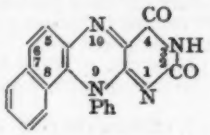
Benzyl-β-naphthylamine couples with the diazonium salt obtained from *p*-toluidine to give 2-*benzylamino*-1-p-*tolueneazonaphthalene*. 1-*Amino*-2-*benzylaminonaphthalene*, obtained by reduction of the azo-compound, can be converted into 9-*benzyl*-5 : 6-*benz*iso*alloxazine* (VII) by the usual procedure.

5 : 6 : 7 : 8-Dibenzalloxazine (VIII, X = O) and its 1 : 3-dimethyl derivative were prepared by the method of Kuhn and Cook (*Ber.*, 1937, **70**, 761), and 2-thio-5 : 6 : 7 : 8-dibenzalloxazine (VIII, X = S) (Robinson and Tomlinson, *J.*, 1935, 467) was also made for testing. The as yet undescribed 2-*imino*-5 : 6 : 7 : 8-*dibenzalloxazine* (VIII, X = NH) has now been obtained by condensation of 2 : 4 : 5-triaminopyrimidine with phenanthraquinone.

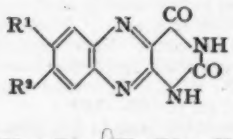
Pyridino(3′ : 2′ : 5 : 6)alloxazine (IX) was prepared by the method of Rudy (*Ber.*, 1938, **71**, 854); this involves the condensation of 5 : 6-diaminoquinoline with alloxan. Rudy admitted that his method of making the diamine, which was similar to that of Kaufman and Zeller (*Ber.*, 1917, **50**, 1626), was somewhat difficult to carry out mainly owing to the variable yields obtained in the nitration of 6-(*p*-toluenesulphonamido)quinoline. We have also experienced difficulty

with this procedure and so a simpler method of preparing the diamine has been developed : this is based on the reduction of 6-*amino*-5-p-*toluene*azoquinoline with stannous chloride (compare Renshaw, Friedman, and Gajewski, *J. Amer. Chem. Soc.*, **1939**, **61**, 3322). There is some confusion in the literature regarding the properties of 5 : 6-diaminoquinoline. Kaufman and Zeller describe it as forming yellow-brown crystals, m. p. 95°; Rudy obtained it as light brown crystals, m. p. 146°, after crystallisation from water in an atmosphere of nitrogen, and after distillation his product had m. p. 150°; and Renshaw *et al.* give the m. p. as 135°. Linkser and Evans have recently (*J. Amer. Chem. Soc.*, 1946, **68**, 874) improved Kaufman and Zeller's method of preparing the diamine dihydrochloride but they did not isolate the free base. As prepared by the method described in this paper, 5 : 6-diaminoquinoline forms golden-yellow, flattened needles, m. p. 149—150°, when crystallised from ether.

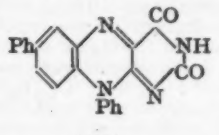
None of the alloxazine derivatives described in this paper has any appreciable effect on the growth of the transplanted Walker rat carcinoma. It was, however, observed that several of the compounds caused pigmentation of the hair of albino rats—a property first described by Haddow *et al.* (*Nature*, **1945**, **155**, 379). These workers found that 9-phenyl-5 : 6-benz*iso*alloxazine was the most effective substance in this respect, though several 9-alkyl-substituted alloxazines exhibited this property to a lesser degree. Of the compounds now tested 9-phenyl-7 : 8-benz*iso*alloxazine causes a salmon-coloured pigmentation of the rat's hair and is as effective as the 5 : 6-benz-derivative, whilst 6 : 9-diphenyl*iso*alloxazine produces an orange coloration and is somewhat less effective, though it is still much more active than the 9-alkyl-5 : 6-benz*iso*alloxazines. Substitution in the 3-position does not reduce the pigmenting power, since it has now been shown that 9-phenyl-3-methyl-5 : 6-benz*iso*alloxazine is as effective as the parent compound. It is noteworthy that in all the really active substances as yet tested there is a 9-phenyl substituent. Neither of the 9-naphthyl*iso*alloxazines is effective.



(I.)



(II*a*; R^1 = Ph, R^2 = H.)
(II*b*, R^1 = H, R^2 = Ph.)



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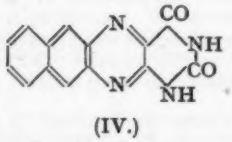

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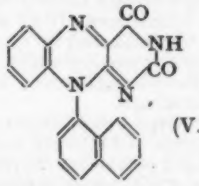

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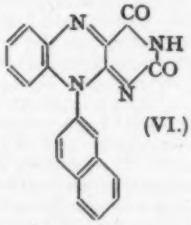

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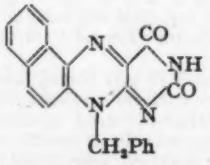
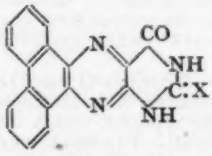
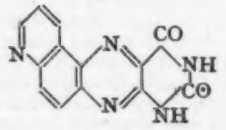


(VII.)



(VIII.)



(IX.)

Experimental.

All m. p.s, which are uncorrected, were determined in sealed capillaries.

2-*Nitro*-1-*anilinonaphthalene*.—50 G. of α-naphthylamine acetate were nitrated as described by Hodgson and Walker (*loc. cit.*) and the product was heated under reflux for one hour with methanolic potassium hydroxide (450 c.c., 5%). The mixture was diluted with water, and the solid which separated was collected and dried. It was then dissolved in glacial acetic acid (1 l.), and concentrated hydrochloric acid (50 c.c.) was added; this caused the precipitation of the hydrochloride of the 4-nitro-compound, which was filtered off and washed with acetic acid. The combined filtrates were diluted with an equal volume of water, whereupon the 2-nitro-amine separated; this was collected by filtration, washed with a little water, and dried. Yield 5 g., m. p. 140—143°. This method of separation was found more convenient than that first described by Hodgson and Walker which involves the solution of the mixed amines in nitrobenzene and subsequent saturation of the solution with hydrogen chloride. 2-Nitro-1-naphthylamine (2 g.), bromobenzene (20 c.c.), potassium carbonate (1·2 g.), and a little cuprous iodide

were refluxed together for 16 hours and then the excess of bromobenzene was removed by steam distillation. The residue was dissolved in benzene, and the solution passed down a short column of activated alumina. When the column was developed by washing with more benzene, a purple band due to the anilino-compound moved slowly down, whilst a red band due to unchanged nitro-amine remained at the top of the column. Evaporation of the benzene eluates gave an orange solid which crystallised from methanol in platelets, m. p. 113—114° (Found: N, 10·2. Calc. for $C_{16}H_{12}O_2N_2$: N, 10·6%). Vesely and Dvorak (*loc. cit.*) give m. p. 110—111°.

2-*Amino*-1-*anilinonaphthalene*.—The above nitro-amine (2 g.) was heated on a steam-bath for 2 hours with a mixture of stannous chloride (8 g.), concentrated hydrochloric acid (40 c.c.), and ethanol (80 c.c.). The solution, which was originally orange-yellow, soon became purple and then slowly decolorised as reduction proceeded. The mixture was diluted with water, and an excess of sodium hydroxide solution was added, after which the product was extracted with ether. The colourless solid obtained by evaporating the dried extract formed small prisms, m. p. 168—169°, from methanol (Found: N, 11·8. Calc. for $C_{16}H_{14}N_2$: N, 11·9%). Harden (*loc. cit.*) gives m. p. 160° and Noelting *et al.* (*loc. cit.*) give 170°. The solution of the base in methanol exhibits a pale blue fluorescence.

9-*Phenyl*-7 : 8-*benziso*-*alloxazine*.—The diamine (1 g.), alloxan (1 g.), boric acid (0·5 g.), and acetic acid (40 c.c.) were heated together on a steam-bath for ½ hour. The solution soon darkened and then deposited an orange-red solid: this solid was collected and recrystallised from acetic acid, giving 9-*phenyl*-7 : 8-*benziso*-*alloxazine* which decomposes at 360—365°. The analytical specimen was dried for 3 hours at 300° (Found: C, 70·8; H, 3·7; N, 16·4. $C_{20}H_{12}O_2N_4$ requires C, 70·6; H, 3·6; N, 16·5%). The alloxazine dissolves in dilute sodium hydroxide to give a light red solution and in acetone to give a yellow solution which exhibits a strong eosin-like fluorescence.

6- *or* 7-*Phenylalloxazine*.—3 : 4-Diaminodiphenyl (1 g.) (Bell and Kenyon, *loc. cit.*) was dissolved in water (25 c.c.) containing concentrated hydrochloric acid (3 c.c.), and the mixture was added to a hot solution of alloxan (1 g.) in water (10 c.c.) which was then heated on a steam-bath for ½ hour. The yellow precipitate of the *alloxazine* was collected, washed with water and then ethanol, and finally dried at 200°/0·001 mm. It decomposed at 335° (Found: N, 19·1. $C_{16}H_{10}O_2N_4$ requires N, 19·3%). The compound dissolves in dilute ammonia solution and to a less extent in acetone: both these solutions show a yellow-green fluorescence.

3-*Nitro*-4-*anilinodiphenyl*.—3-Nitro-4-aminodiphenyl (1·5 g.), potassium carbonate (0·9 g.), bromobenzene (10 c.c.), and a little cuprous iodide were heated together for 10 hours and then the excess of bromobenzene was removed by distillation in steam. A solution of the solid residue in benzene was percolated through a column of activated alumina. Early eluates contained an orange-red solid; this was 3-*nitro*-4-*anilinodiphenyl*, which crystallised from methanol in orange plates, m. p. 137—138° (Found: N, 9·9. $C_{18}H_{14}O_2N_2$ requires N, 9·7%). Further washing of the chromatographic column with benzene gave unchanged nitro-amine, m. p. 165—167°.

6 : 9-*Diphenyliso*-*alloxazine*.—The above nitro-base (1 g.), granulated tin (4 g.), ethanol (30 c.c.), and concentrated hydrochloric acid (15 c.c.) were heated together under reflux for 2 hours. After dilution with water, an excess of sodium hydroxide solution was added and the mixture was extracted with ether. The colourless oil obtained by evaporating this extract did not solidify, and so it was dissolved in glacial acetic acid (30 c.c.) and heated under reflux with alloxan (1 g.) and boric acid (0·5 g.). After one hour, water was added and the brown precipitate was collected by filtration. The *alloxazine* was crystallised from acetic acid, forming orange-brown flattened needles which decomposed at 380° (Found: N, 14·8. $C_{22}H_{14}O_2N_4$ requires N, 15·3%). 6 : 9-Diphenyl*iso*alloxazine is slightly soluble in acetone and the solution exhibits a brilliant yellow-green fluorescence.

3-*Nitro*-4-(1′-*naphthylamino*)*diphenyl*.—3-Nitro-4-aminodiphenyl (3 g.), α-bromonaphthalene (5 g.), fused potassium acetate (3 g.), and cupric acetate (0·2 g.) were heated together at the b. p. of the mixture for 4 hours. The product was boiled with light petroleum (b. p. 60—80°), and the extract passed down a short column of activated alumina. The red gum which remained was then dissolved in benzene, and this solution was poured on to the same column which was then developed by washing with more benzene. The first colourless eluates contained all the unchanged bromonaphthalene, and as a deep purple band moved off the column the eluates became orange-coloured and contained the required *nitro-diphenyl*. This formed scarlet plates, m. p. 146—147°, when crystallised from methanol (Found: N, 8·1. $C_{22}H_{16}O_2N_2$ requires N, 8·2%).

3-*Amino*-4-(1′-*naphthylamino*)*diphenyl*.—3-Nitro-4-(1′-naphthylamino)diphenyl (1 g.), Raney nickel catalyst (1 g.), and ethanol (100 c.c.) were shaken in an atmosphere of hydrogen until no further uptake of gas was observed (about 8 hours). The solution, which was originally orange-coloured, gradually became colourless and deposited a white solid. This solid, which was sparingly soluble in alcohol and ether, was dissolved by adding acetone and then boiling off the ether. The solution was filtered to remove the catalyst and then concentrated under reduced pressure. The *diamine*, crystallised from methanol–chloroform or methanol–acetone, separated in the form of colourless prisms, m. p. 184—185° (Found: N, 8·6. $C_{22}H_{18}N_2$ requires N, 9·0%). When the diamine (2 g.), alloxan (2 g.), and acetic acid (120 c.c.) were heated together for 2 hours the only isolatable product was the unchanged diamine.

6 : 7-*Benzalloxazine*.—2 : 3-Diaminonaphthalene (2 g.) was dissolved in water (75 c.c.) containing concentrated hydrochloric acid (5 c.c.). The solution was boiled with a little charcoal (to remove coloured impurity) and then filtered. Alloxan (2 g.), dissolved in water (25 c.c.), was added to the colourless filtrate, and the mixture was boiled for 10 minutes, a paste of orange-red solid then having formed. The product was collected by filtration, washed well with water and then alcohol, and finally dried in a steam-oven. The compound sublimed at 280°/0·001 mm., forming deep red prisms which decomposed at 385° [Found: (for material dried at 100°) C, 61·2; H, 3·4; (for the sublimed substance) C, 63·8; H, 3·0. $C_{14}H_8O_2N_4$ requires C, 63·6; H, 3·05%). 6 : 7-*Benzalloxazine* dissolves in dilute ammonia solution and in acetone: the former solution shows a reddish-blue fluorescence, and the latter an orange-yellow fluorescence.

1-(2′-*Nitroanilino*)*naphthalene*.—*p*-Nitroaniline (2 g.), α-bromonaphthalene (10 c.c.), potassium

carbonate (2 g.), and a small amount of cuprous iodide were heated together for 3 hours. The product was purified by the chromatographic method described above: it formed orange prismatic needles, m. p. 158—159°, when crystallised from methanol (Found: N, 10·3. Calc. for $C_{16}H_{13}O_2N_3$: N, 10·6%). Waldman and Beck (*loc. cit.*) give m. p. 155° for the product obtained by heating *o*-bromoaniline with α-naphthylamine.

1-(2′-*Aminoanilino*)*naphthalene*.—The above nitro-amine (2·5 g.) was reduced in ethanol solution by aid of a Raney nickel catalyst in the manner already described: reduction was complete in one hour. The oil obtained after evaporating the filtered ethanolic solution solidified on rubbing with light petroleum (b. p. 60—80°). The diamine (1·5 g.) crystallised from benzene–light petroleum in well-defined prismatic tablets, m. p. 136—138° (Found: N, 11·9. Calc. for $C_{16}H_{14}N_2$: N, 11·9%). Waldman and Beck (*loc. cit.*) give m. p. 135°. The colourless solid is quite stable, but solutions of the diamine readily darken in air.

9-(1′-*Naphthyl*)iso*alloxazine*.—The diamine (0·5 g.) was dissolved in acetic acid (20 c.c.) containing concentrated hydrochloric acid (1 c.c.), and after addition of alloxan (0·5 g.) in water (2 c.c.) the mixture was heated on a steam-bath for one hour. The orange-brown crystals which had separated were collected and washed with a little methanol. On recrystallisation from acetic acid the *naphthyliso-alloxazine* formed deep yellow needles which decomposed at 265° (Found: N, 15·9. $C_{20}H_{12}O_2N_4$ requires N, 16·4%). The substance dissolved in dry acetone to give a yellow non-fluorescent solution but on addition of water a deep blue fluorescence developed.

2-(2′-*Nitroanilino*)*naphthalene*.—*o*-Nitroaniline (3 g.), β-chloronaphthalene (7 g.), fused potassium acetate (3 g.), and cupric acetate (0·1 g.) were heated together under reflux for 3 hours. The unchanged chloronaphthalene was removed by chromatographic separation, and the required compound was crystallised from methanol; it formed long prismatic orange needles, m. p. 112—113° (Found: N, 10·7. Calc. for $C_{16}H_{12}O_2N_2$: N, 10·6%). Warren and Smiles (*loc. cit.*) give m. p. 110°.

2-(2′-*Aminoanilino*)*naphthalene*.—The nitro-amine was catalytically reduced as previously described, and the residue obtained by evaporation of the ethanol was crystallised from light petroleum (b. p. 60—80°), from which it formed colourless prismatic needles, m. p. 84—85° forming a cloudy melt which cleared at 100° (Found: N, 12·0. $C_{16}H_{14}N_2$ requires N, 11·9%).

9-(2′-*Naphthyl*)iso*alloxazine*.—This *alloxazine* was formed from the above *diamine* in the usual way and was obtained as an orange microcrystalline powder which decomposed at 280° (Found: N, 16·0. $C_{20}H_{12}O_2N_4$ requires N, 16·4%).

Benzyl-β-naphthylamine.—β-Naphthylamine (5 g.), benzaldehyde (5 c.c.), and methanol (75 c.c.) were warmed for ½ hour on a steam-bath by which time all the material had passed into solution. The cooled solution deposited 7 g. of benzylidene-β-naphthylamine, m. p. 102°. This was dissolved in ethanol (100 c.c.), Raney nickel catalyst (2 g.) added, and the mixture shaken in an atmosphere of hydrogen. The theoretical amount of gas was absorbed during 2 hours and then the solution was filtered and evaporated. The colourless residue (6 g.) crystallised from light petroleum (b. p. 60—80°) in prisms, m. p. 68°.

2-*Benzylamino*-1-p-*tolueneazonaphthalene*.—A solution of the diazonium salt obtained by adding sodium nitrite (1·75 g.) to *p*-toluidine (2·7 g.) dissolved in a mixture of concentrated hydrochloric acid (8 c.c.) and water (25 c.c.) was added to a cooled solution of benzyl-β-naphthylamine (6 g.) in ethanol (300 c.c.). After a short time an orange solid began to separate, and the mixture was left in an ice-chest overnight to complete the reaction. The *azo*-compound was collected and recrystallised from methanol, forming long, orange-red needles (8 g.), m. p. 105—106° (Found: C, 82·3; H, 6·2; N, 12·5. $C_{24}H_{21}N_3$ requires C, 82·1; H, 6·0; N, 12·0%).

1-*Amino*-2-*benzylaminonaphthalene*.—A solution of stannous chloride (20 g.) in concentrated hydrochloric acid (30 c.c.) was added to a solution of the azo-compound in ethanol (300 c.c.) and the mixture was warmed on a steam-bath until the colour was discharged (about 30 minutes). After dilution with water, an excess of 10N-sodium hydroxide was added, and the cooled mixture was extracted with ether. The ethereal extract, which showed a strong yellow-green fluorescence, was dried and evaporated. When the residue was crystallised from light petroleum (b. p. 60—80°) the *diamine* was obtained as colourless prisms, m. p. 86—87° (Found: C, 81·9; H, 6·4. $C_{17}H_{16}N_2$ requires C, 82·2; H, 6·5%). Solutions of the diamine rapidly darken in contact with air.

9-*Benzyl*-5 : 6-*benziso*alloxazine.—The benzyldiamine (1 g.), alloxan (1·5 g.), and boric acid (2·0 g.) were dissolved in glacial acetic acid (70 c.c.), and the solution heated under reflux for 30 minutes. Careful dilution of the mixture with water caused precipitation of short orange-brown needles (0·6 g.). 9-*Benzyl*-5 : 6-*benziso*alloxazine formed orange needles, decomposing at 295°, when recrystallised from acetic acid (Found: C, 70·9, 71·0; H, 4·5, 4·5. $C_{21}H_{14}O_2N_4$ requires C, 71·2; H, 4·0%). The alloxazine dissolved in dilute sodium hydroxide solution to give a yellow solution and in acetone or methanol to give a strongly fluorescent solution (yellow-green).

2-*Imino*-5 : 6 : 7 : 8-*dibenzalloxazine*.—The bisulphite compound of 2 : 4 : 5-triaminopyrimidine (prepared by the method of Totter, *J. Biol. Chem.*, 1944, **152**, 147) was suspended in water, and dilute sulphuric acid added. After a short time the insoluble sulphate was collected, and 2 g. of this salt were heated in acetic acid (100 c.c.) with phenanthraquinone (2 g.), the mixture being gently boiled for 15 minutes by which time a buff-coloured solid had separated. This was the required *iminoalloxazine*; it decomposed when heated above 400° (Found: N, 22·2. $C_{16}H_{11}ON_5$ requires N, 22·4%).

6-*Amino*-5-p-*tolueneazoquinoline*.—6-Nitroquinoline (Cook, Heilbron, and Steger, *J.*, 1943, 416) was reduced in ethanol solution in the presence of a palladium–strontium carbonate catalyst (compare Rudy, *Ber.*, 1938, **71**, 854). 6-Aminoquinoline (1·44 g.) was dissolved in ethanol (50 c.c.), and to the ice-cooled solution was added the diazonium salt prepared from *p*-toluidine (1·07 g.) dissolved in water (10 c.c.) containing concentrated hydrochloric acid (3 c.c.), and a solution of sodium nitrite (0·7 g.) in water (5 c.c.). The mass of red crystals which separated overnight was collected by filtration and washed with a little methanol. The *azo*-compound formed red flattened needles, m. p. 245° (decomp.), when crystallised from methanol (Found: N, 21·4. $C_{16}H_{14}N_4$ requires N, 21·4%).

Pyridino(3′ : 2′ : 5 : 6)*alloxazine.*—The azo-compound (0·8 g.) was dissolved in concentrated hydrochloric acid (12 c.c.), and after the addition of stannous chloride (4 g.) the mixture was heated on a steam-bath. The solution at first assumed a deep carmine colour but as reduction proceeded a light orange colour developed and a solid separated. When no further lightening of the colour occurred, more hydrochloric acid (5 c.c.) was added and the mixture was cooled in ice. The crystalline product was filtered off and washed with methanol. The free base was obtained by dissolving the dihydrochloride in water and then covering the solution with a layer of ether; an excess of sodium hydroxide solution was then added, and the mixture well shaken. The dried ethereal extract was concentrated until golden-yellow flattened needles of 5 : 6-diaminoquinoline separated. After a further crystallisation from ether the product had m. p. 149—150°. Pyridinoalloxazine was prepared from the diamine by the method of Rudy (*loc. cit.*); it formed a yellow microcrystalline powder, decomposing above 400°, when crystallised from formic acid.

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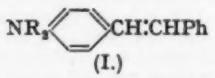
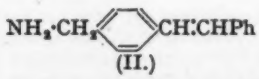
56. 4-*Styrylbenzylamine and* 4-*Styrylbenzyldimethylamine.*

By GEORGE A. R. KON.

The *bases* (II) and (III) have been prepared in order to compare their growth- and tumour-inhibiting activity with that of basically substituted stilbenes such as (I). In the course of preparation of (II) an abnormal Hofmann degradation, leading to the formation of an amide, has been noted.

CERTAIN stilbenes with a basic substituent in one of the para-positions such as 4-dimethylaminostilbene (I, R = Me) are carcinogenic and have a marked power of inhibiting the growth of transplanted tumours in the rat (Haddow, Harris, and Kon, *Biochem. J.*, 1945, **39**, ii). A description of a number of such compounds will be published shortly; in the meantime it appeared of interest to prepare the compounds (II) and (III) for comparison with those of type (I) as regards their biological properties, and more especially to ascertain whether the activity of such compounds could be connected with their ability to assume a quinonoid form. The compounds (II) and (III) are related to those of type (I) in the same way as " Marfanil " is related to sulphanilamide.


(I.)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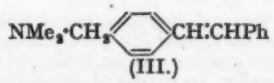
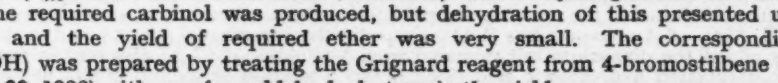

(III.)

A number of routes to the compounds (II) and (III) were explored. The most direct, reduction of 4-cyanostilbene (Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103), was unsuccessful. It seemed probable that stilbene with a suitable substituent for conversion into (II) or (III) might be formed by diazotising a derivative of *p*-aminobenzyl alcohol and coupling it with cinnamic acid by the general method of Meerwein, Büchner, and van Emster (*J. pr. Chem.*, 1939, **152**, 237):


(IV.) (V.) (VI.)

Thus, the *ether* (V, R = OMe) should have been formed from *p*-aminobenzyl methyl ether, but no stilbene was produced when the Meerwein reaction was applied to this compound or to *p*-aminobenzyl cyanide, *p*-aminophenylacetic acid, and ethyl *p*-aminophenylacetate. An alternative method of preparing the same ether is by treatment of *p*-(ω-methoxymethyl)benzaldehyde (VI) (Quélet, *Bull. Soc. chim.*, 1933, **53**, 222) with benzylmagnesium chloride. A good yield of the required carbinol was produced, but dehydration of this presented unexpected difficulties and the yield of required ether was very small. The corresponding *alcohol* (V, R = OH) was prepared by treating the Grignard reagent from 4-bromostilbene (Anschütz, *Ber.*, 1927, **60**, 1322) with paraformaldehyde, but again the yield was very poor.

The method finally adopted was the degradation of 4-*styrylphenylacetic acid* or its *amide*. The acid could be prepared by two alternative routes: in the first, *p*-aminoacetophenone was

converted by the Meerwein reaction into *4-styrylphenyl methyl ketone*, $CHPh{:}CH{\cdot}C_6H_4{\cdot}COMe(p)$. This was subjected to the Willgerodt reaction, but the yield of the *amide* (V, R = $CO{\cdot}NH_2$) was very low and the separation of it from sulphur difficult; however, the Kindler modification of the reaction afforded a good yield of the corresponding *thiomorpholide*, which gave styrylphenylacetic acid on hydrolysis. In the alternative process, *p*-aminobenzoic acid was converted by the Meerwein reaction into *stilbene-4-carboxylic acid*, the methyl and ethyl esters of which had already been obtained from the corresponding aminobenzoic esters by Fuson and Cooke (*J. Amer. Chem. Soc.*, 1940, **62**, 1180). In agreement with their observation, the Meerwein reaction proceeds satisfactorily with amines carrying a negative substituent in the para-position, as in this instance. The acid was converted through its chloride into the crystalline *diazo-ketone*, and this subjected to the Wolff rearrangement to give a good yield of 4-styrylphenylacetamide, which could be hydrolysed to the acid if required.

The Hofmann degradation of this amide, which should have given the amine (II), gave an unexpected result: the products were 4-cyanostilbene and *stilbene-4-carboxyamide*, the latter being the principal product, whilst no trace of amine was isolated. The formation of nitriles by oxidation of the amines initially formed in the Hofmann reaction has already been recorded, notably in acetylenic derivatives (Rinkes, *Rec. Trav. chim.*, 1920, **39**, 704; compare "Organic Reactions", Vol. III, 276, New York, John Wiley and Sons Inc.), but the production of the next lower homologue of the amide appears to be novel.

Styrylphenylacetic acid was converted by way of the chloride into the azide, which on treatment with alcohol passed smoothly into *ethyl 4-styrylbenzylcarbamate* (V, R = $NH{\cdot}CO_2Et$). This was exceptionally resistant to hydrolysis with acids, but gave the desired *amine* (II) on alkaline hydrolysis.

For the preparation of the amine (III) 4-methylstilbene was brominated in the side chain by means of *N*-bromosuccinimide (Schmid and Karrer, *Helv. Chim. Acta*, 1946, **29**, 573) and the *bromide* treated with excess of dimethylamine; the amine (II) could also be obtained from the bromide by the action of alcoholic ammonia.

Experimental.

4-Styrylbenzylmethyl Ether.—7·5 G. of *p*-(ω-methoxymethyl)benzaldehyde in dry ether were gradually added to a rapidly stirred Grignard reagent prepared from 7·9 g. of benzyl chloride (20% excess). The reaction product was decomposed with ammonium chloride solution, and the dried ethereal layer evaporated. The residue was dissolved in 50 c.c. of benzene and boiled with 25 g. of phosphoric oxide for ½ hour. The solution was then diluted with light petroleum and percolated through a short column of activated alumina (Spence, type H), evaporated, and the residue distilled, the greater part boiling at 190—230°/1 mm. (5·8 g.). The colourless distillate partly solidified, and the *ether* was freed from oil by rubbing with light petroleum (b. p. 40—60°) and crystallised from methyl alcohol in plates, m. p. 78° (Found: C, 85·5; H, 7·2. $C_{16}H_{16}O$ requires C, 85·7; H, 7·2%). The petroleum washings contained another compound, evidently a hydrocarbon, which crystallised from methyl alcohol in plates, m. p. 108° (Found: C, 92·4; H, 7·6%). In a second preparation the *carbinol* first formed was isolated and boiled at 190—192°/2·5 mm. (7·8 g. from 9·1 g. of aldehyde) (Found: C, 79·5; H, 7·6. $C_{16}H_{18}O_2$ requires C, 79·3; H, 7·5%). On dehydration this gave the hydrocarbon as sole product.

4-Styrylbenzyl Alcohol.—10 G. of *p*-bromostilbene (conveniently prepared from *p*-bromoaniline by the Meerwein process) were boiled under reflux with 1 g. of magnesium turnings, activated by heating with iodine, and 50 c.c. of dry ether for 2 hours; only a small part of the metal dissolved. 5 G. of carefully dried paraformaldehyde were added, and the refluxing continued overnight. The reaction mixture was decomposed with dilute sulphuric acid, the ether layer dried and evaporated, and the residue taken up in light petroleum (b. p. 60—80°) and percolated through a column of activated alumina, the column being washed with the same solvent. Unchanged bromostilbene was recovered from the percolate. On stripping the column with ether containing methanol, a semi-solid mass was recovered which did not crystallise easily and was therefore re-chromatographed in benzene solution. On stripping the column, 0·6 g. of the *alcohol* was recovered, and crystallised from benzene in plates, m. p. 160—161° (Found: C, 85·9; H, 7·0. $C_{15}H_{14}O$ requires C, 85·5; H, 6·7%).

4-Styrylphenyl Methyl Ketone.—An ice-cold solution of 50 g. of *p*-aminoacetophenone in 100 c.c. of concentrated hydrochloric acid and 100 g. of ice was stirred and diazotised with 25·5 g. of sodium nitrite in the minimum of water. To this solution was added an ice-cold solution of 55 g. of cinnamic acid in 350 c.c. of acetone, followed by 70 g. of sodium acetate and 15·5 g. of cupric chloride in 45 c.c. of water. A slight rise in temperature soon occurred. The mixture was left overnight, then distilled in steam to remove acetone and volatile by-products of the reaction. After cooling, a brown solid was collected, which was dissolved in benzene, freed from cinnamic acid by extraction with alkali, and then washed, dried, and percolated through a column of activated alumina, the column being repeatedly developed with more benzene. On removal of the solvent, 36·7 g. of the *ketone* were recovered and crystallised from alcohol, then from benzene–petroleum, forming plates, m. p. 141—142° (Found: C, 86·5; H, 6·1. $C_{16}H_{14}O$ requires C, 86·4; H, 6·3%).

4-Styrylphenylacet-thiomorpholide.—11·1 G. of the above ketone were gently boiled with 4 g. of sulphur and 8·7 g. of morpholine for 2 hours (oil-bath), the contents of the flask dissolved in chloroform, and the solution well washed with water, dried, and evaporated, yielding 7·5 g. of the *thiomorpholide*

after crystallisation from ethyl acetate; it formed lemon-yellow leaflets, m. p. 177—178° (Found: C, 74·3; H, 6·4. $C_{29}H_{31}ONS$ requires C, 74·3; H, 6·6%). The compound is very resistant to alkaline hydrolysis.

4-Styrylphenylacetic Acid.—5·4 G. of the thiomorpholide were boiled over-night with 200 c.c. of acetic acid and 80 c.c. of hydrochloric acid, and the solution cooled and diluted with water, precipitating the *acid*. This was crystallised from acetic acid, then from methyl alcohol containing a little water, and melted at 186—187° (Found: C, 80·4; H, 6·0. $C_{16}H_{14}O_2$ requires C, 80·6; H, 5·9%). The *anilide* crystallised from alcohol in small needles, m. p. 195—196° (Found: C, 84·1; H, 6·1. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1%).

Stilbene-4-carboxylic Acid.—66 G. of *p*-aminobenzoic acid were diazotised and treated with cinnamic acid exactly as described on p. 225. The precipitated acid was extracted with hot water to remove cinnamic acid, and the residue crystallised from acetic acid, the first crop weighing 48 g.; more was obtained from the mother-liquors. The *acid* crystallised from acetic acid or from alcohol in plates, m. p. 243—244° (Found: C, 80·4; H, 5·7. $C_{15}H_{12}O_2$ requires C, 80·3; H, 5·4%). On treatment with ethereal diazomethane it formed the methyl ester, m. p. 157° (Fuson and Cooke, *loc. cit.*, give 158—159°). The *anilide* crystallised from alcohol in small needles, m. p. 204—205° (Found: C, 84·1; H, 5·7. $C_{21}H_{17}ON$ requires C, 84·3; H, 5·7%).

4-Styrylphenylacetamide.—The crude chloride prepared by warming the above acid with thionyl chloride had m. p. 125—126°. A dry ethereal solution of this (from 7 g. of acid) was added to dry ethereal diazomethane (0·1 mol.). After an hour the *diazo-ketone* began to separate, the process being completed over-night (yield 3·8 g.; in another run 11 g. of acid gave 7·8 g. of diazo-ketone). It crystallised from benzene–petroleum in fern-like aggregates of buff needles, m. p. 150—152° (Found: C, 77·4; H, 5·0. $C_{16}H_{13}ON$ requires C, 77·1; H, 5·3%). 2·2 G. of the ketone in 20 c.c. of dioxan were boiled under reflux with 16·5 c.c. of ammonia (*d* 0·88) and 3·3 c.c. of 10% aqueous silver nitrate for 2 hours. Water was then added, and the *amide*, formed in almost quantitative yield, was filtered off and crystallised from dioxan–water or from acetic acid (charcoal). It formed silvery plates, m. p. 258° (Found: C, 80·7; H, 6·4. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3%). An attempt to convert the diazo-ketone directly into styrylphenylacetic acid by treating it with silver oxide in presence of sodium carbonate and sodium thiosulphate in aqueous solution was unsuccessful, most of the ketone being recovered unchanged. The acid (1·6 g.) was readily obtained when 2 g. of amide were boiled for 3 hours with 50 c.c. of acetic acid and 50 c.c. of hydrochloric acid, and the solution diluted. The amide was also obtained, though in very poor yield, on heating styrylphenyl methyl ketone with ammonium polysulphide in a sealed tube.

Hofmann Degradation.—10·8 G. of bromine were gradually added to an ice-cold solution of 10·2 g. of potassium hydroxide in 100 c.c. of water, and the solution added to 11 g. of finely powdered styrylphenylacetamide with rapid mechanical stirring. 14·4 G. of potassium hydroxide in 25 c.c. of water were added, and the mixture kept rapidly stirred at 80° for 1½ hours. It was cooled and diluted, and the solid filtered off and crystallised from alcohol. The first two crops of crystals were recrystallised from acetic acid, giving 4 g. of the *amide*, which separated from benzene–petroleum in large plates, m. p. 157° (Found: C, 80·9, 80·9; H, 5·9, 6·1. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8%); on hydrolysis with acetic–hydrochloric acid it gave stilbenecarboxylic acid, m. p. and mixed m. p. 243°. The mother-liquors from which the amide had separated were diluted, a more fusible substance separating. As it did not crystallise readily, it was twice chromatographed in petroleum solution, then crystallised from this solvent; several crops of crystals, m. p. 115—116°, were obtained and identified as 4-cyanostilbene (mixed m. p.) (Found: C, 88·1; H, 5·2. Calc.: C, 87·8; H, 5·4%). The substance for comparison had been prepared in good yield from *p*-aminobenzonitrile by the Meerwein method, which is preferable to the method used by Ashley *et al.* (*loc. cit.*) (unpublished observation by Dr. R. J. C. Harris).

Modified Hofmann Degradation.—0·7 G. of the amide in 9 c.c. of methyl alcohol were mixed with a solution of 0·25 g. of sodium in 7·5 c.c. of methyl alcohol, and the ice-cold solution treated with 0·2 c.c. of bromine. After an hour at room temperature the mixture was warmed for 10 minutes on the steam-bath, cooled, the unchanged amide filtered off, and the solution evaporated. The small amount of solid obtained crystallised from methyl alcohol, m. p. 165°, and was evidently *methyl 4-styrylphenylmethylcarbamate* (Found: C, 76·9; H, 6·3. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4%).

Curtius Degradation.—1·6 G. of styrylphenylacetic acid were converted into the chloride by warming with excess of thionyl chloride, which was then distilled off and the last traces removed by repeated evaporation with chloroform under reduced pressure. The chloride in 30 c.c. of acetone was treated with 0·56 g. of sodium azide in the minimum of water with ice-cooling. After 15 minutes the solution was diluted with water, precipitating the azide in almost quantitative yield. It was comparatively stable and could be recrystallised from benzene; it melted at 260—265° (decomp.). The crude azide was warmed for 5 minutes with 10 vols. of alcohol; solution took place and there was a steady evolution of gas. The solution was concentrated and diluted with water, precipitating *ethyl 4-styrylbenzylcarbamate* in good yield. It crystallised from dilute methyl or ethyl alcohol in needles, m. p. 146—147° (Found: C, 77·0; H, 6·9. $C_{18}H_{19}O_2N$ requires C, 76·9; H, 6·8%).

4-Styrylbenzylamine.—The above urethane was not hydrolysed by heating for 24 hours with concentrated hydrochloric acid in a sealed tube at 170—180°. 1·8 G. were boiled with 20 c.c. of alcohol and 5 g. of potassium hydroxide in 10 c.c. of water under reflux for 1½ hours. Some alcohol was distilled off, and hot water gradually added; as this caused a precipitate, 20 c.c. of alcohol were added and the boiling continued for a further 2½ hours. The solution was diluted, and strongly acidified with hydrochloric acid to ensure the elimination of carbon dioxide. Some solid, evidently the hydrochloride of the amine, was precipitated and was filtered off, the liquid and solid being separately basified and extracted with ether. After removal of the solvent the *base* (0·45 g.) was crystallised from benzene–petroleum or from *cyclo*hexane, forming plates, m. p. 130° (Found: C, 86·2; H, 7·1. $C_{15}H_{15}N$ requires C, 86·1; H, 7·2%). The hydrochloride crystallised from acetic acid in silvery leaflets, m. p. 300—305° (decomp.). The *benzoyl* derivative crystallised from alcohol in lustrous plates, m. p. 205—206° (Found: C, 84·1; H, 6·2. $C_{22}H_{19}ON$ requires C, 84·3; H, 6·1%).

4-Bromomethylstilbene.—8·4 G. of *p*-methylstilbene, 7·8 g. of *N*-bromosuccinimide, 50 mg. of benzoyl peroxide, and 30 c.c. of carbon tetrachloride were boiled under reflux for 3 hours. After the precipitated succinimide had been filtered off, the solution was washed with water, dried, and evaporated. The residue was crystallised from alcohol, then from petroleum, forming small needles (5·8 g.), m. p. 117—118° depressed by the starting material, which had the same m. p. The analytical figures suggest a slight contamination with a hydrocarbon (Found : C, 66·7; H, 4·9; Br, 28·6. $C_{15}H_{13}Br$ requires C, 65·9; H, 4·8; Br, 29·3%).

The bromide is evidently easily hydrolysed to the alcohol : a specimen prepared in a pilot experiment and containing much unchanged methylstilbene was chromatographed in light petroleum. The stilbene was recovered from the percolate, and on eluting the column with ether–methanol pure hydroxymethylstilbene was recovered, m. p. and mixed m. p. 160—161° (Found : C, 85·7; H, 6·7. Calc. : C, 85·5; H, 6·7%); no trace of the bromide was recovered.

4-Styrylbenzyldimethylamine.—5 G. of the above bromide were kept for 3 days with 200 c.c. of alcohol and 8 c.c. of dimethylamine, a clear solution being formed. The alcohol was then evaporated off, the diluted residue treated with hydrochloric acid, extracted with ether to remove non-basic material, then strongly basified, and the *base* extracted with ether. The dried ethereal solution was evaporated, and the residue dissolved in petroleum and percolated through a column of alumina. The base, recovered in good yield, was very soluble but could be crystallised from petroleum (b. p. 30—40°) or very little methanol, forming large plates, m. p. 86—87° (Found : C, 86·1; H, 8·2. $C_{17}H_{19}N$ requires C, 86·0; H, 8·1%). The *picrate* formed yellow plates from alcohol, m. p. 146° (decomp.) (Found : C, 59·2; H, 4·8. $C_{23}H_{22}O_7N_4$ requires C, 59·2; H, 4·8%).

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57. *Reactions of α-Cyanoprene (1-Cyanobuta-1 : 3-diene). Part I. Addition of Nitro-paraffins.**

By (MRS.) J. L. CHARLISH, W. H. DAVIES, and J. D. ROSE.

Nitroethane, 1- and 2-nitropropane, and nitro*cyclo*hexane react with α-cyanoprene (1-cyanobuta-1 : 3-diene) in the presence of a basic catalyst to give 5-substituted 5-nitropentenyl cyanides [NO_2·CRR′·CH_2·CH:CH·CH_2·CN]. Nitroethane and nitromethane also add respectively to two and three moles of α-cyanoprene. Some of the products are hydrogenated over palladium on calcium carbonate to saturated nitro-cyanides, and over Raney nickel to amino-cyanides and diamines, and are reduced with iron and acid to unsaturated amino-cyanides. Amino- and nitro-acids are also prepared by hydrolysis of the appropriate cyanides. Treatment of the 2-nitropropane adduct, *5-nitro-5-methylhex-2-enyl cyanide*, with secondary amines (*e.g.*, morpholine) gives the $\Delta^1(?)$-*isomer*, together with, *e.g.*, *5-nitro-2-morpholino-5-methylhexyl cyanide*.

BRUSON and his co-workers (*J. Amer. Chem. Soc.*, 1942, **64**, 2547, 2850; 1943, **65**, 18, 23) have shown that a wide variety of compounds containing active hydrogen atoms can be added to vinyl cyanide. The synthetic value of this " cyanoethylation " reaction prompted interest in the possibility of extending it to α-cyanoprene (1-cyanobuta-1 : 3-diene) (I). If α-cyanoprene formed 1 : 4-adducts with compounds containing active hydrogen, this would offer a synthetic method for the introduction of a straight chain of five carbon atoms into many organic substances.

α-Cyanoprene was first prepared, though in poor yield, by Coffman (*J. Amer. Chem. Soc.*, 1935, **57**, 1981), by interaction of 1-chlorobuta-2 : 3-diene with sodium cyanide in methyl alcohol. Coffman confirmed the structure of the product by hydrolysis to 2-vinylacrylic acid and by reduction to *n*-amylamine. A better method of preparation was later reported by Gudgeon, Hill, and I.C.I. Ltd. (E.P. 515,737); this involved the pyrolysis of esters of crotonaldehyde cyanohydrin at about 500°. The α-cyanoprene used in this work was prepared by pyrolysis of crotonaldehyde cyanohydrin acetate.

As by-products in his preparation of α-cyanoprene, Coffman isolated two liquids, one of which was shown to be 4-methoxybut-2-enyl cyanide (II) and the other an addition product with two moles of methyl alcohol (either III or IV).

CH_2:CH·CH:CH·CN (I.)

MeO·CH_2·CH:CH·CH_2·CN (II.)

MeO·CH_2·CH(OMe)·CH_2·CH_2·CN (III.)

MeO·CH_2·CH_2·CH(OMe)·CH_2·CN (IV.)

* Patent protection pending.

The second product was also obtained by heating α-cyanoprene with methyl alcohol in the presence of sodium methoxide. Coffman also obtained ethyl 4-chlorobut-2-ene-1-carboxylate ($CH_2Cl{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CO_2Et$) by the interaction of α-cyanoprene with hydrogen chloride.

Similar addition reactions have now been carried out with primary and secondary nitro-paraffins, which add readily to α-cyanoprene in the presence of a basic catalyst. For most of the reactions described, methyltriethylammonium hydroxide has been used as catalyst and dioxan as solvent, but other bases (sodium hydroxide or methoxide) are effective, and alcohol can be used as a solvent as the rate of addition of alcohols to α-cyanoprene is low.

2-Nitropropane reacted with α-cyanoprene to give an adduct *A* or *B*, according to whether 1 : 4- or 1 : 2-addition had occurred.

$NO_2{\cdot}CMe_2{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CN$ (*A*.) $\qquad$ $CH_2{:}CH{\cdot}CH(CMe_2{\cdot}NO_2){\cdot}CH_2{\cdot}CN$ (*B*.)

This adduct, after ozonisation followed by treatment with hydrogen peroxide, gave an acid, $C_4H_8(NO_2){\cdot}CO_2H$, m. p. 103—104°, thus excluding the possibility of an acid derived from *B*. The acid must therefore be β-nitro*iso*valeric acid (XX) though no m. p. has previously been recorded and attempts to repeat the literature preparations (Bredt, *Ber.*, 1881, **14**, 1782; 1882, **15**, 2319; Dessaignes, *Annalen*, 1851, **79**, 374) have been unsuccessful.

This result, taken in conjunction with the fact that 1 : 4-addition to α-cyanoprene has been established in the cases of methyl alcohol and hydrochloric acid (Coffman, *loc. cit.*), acetylacetone, and ethyl malonate (Part II, following paper), has led us to formulate all the nitro-paraffin derivatives as 1 : 4-adducts. Further confirmation followed from the reduction of the adducts: if 1 : 2-addition had occurred, the resulting 2-nitrocyanides would hydrogenate to give pyrrole derivatives (cf. Buckley and Elliot, *J.*, 1947, 1508), whereas normal reduction to open chain compounds was obtained with all the cyanoprene adducts.

The adduct from 2-nitropropane is therefore *5-nitro-5-methylhex-2-enyl cyanide* (*A*). Similarly, 1-nitropropane and nitro*cyclo*hexane gave *5-nitrohept-2-enyl cyanide* (type V) and 4-(1-*nitro*cyclo*hexyl*)*but-2-enyl cyanide* (type V), respectively.

$$CH_2{:}CH{\cdot}CH{:}CH{\cdot}CN + NO_2{\cdot}CHRR' \longrightarrow NO_2{\cdot}CRR'{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CN \qquad (V.)$$

With nitroethane both the mono-adduct, *5-nitrohex-2-enyl cyanide* (V; R = Me, R′ = H), and the bis-adduct, *5-nitro*-1 : 9-*dicyano*-*5-methylnona*-2 : 7-*diene* (VI) were obtained; from nitromethane, only the tris-adduct (VII) could be isolated. (VII) was unstable and was characterised as its hexahydro-derivative.

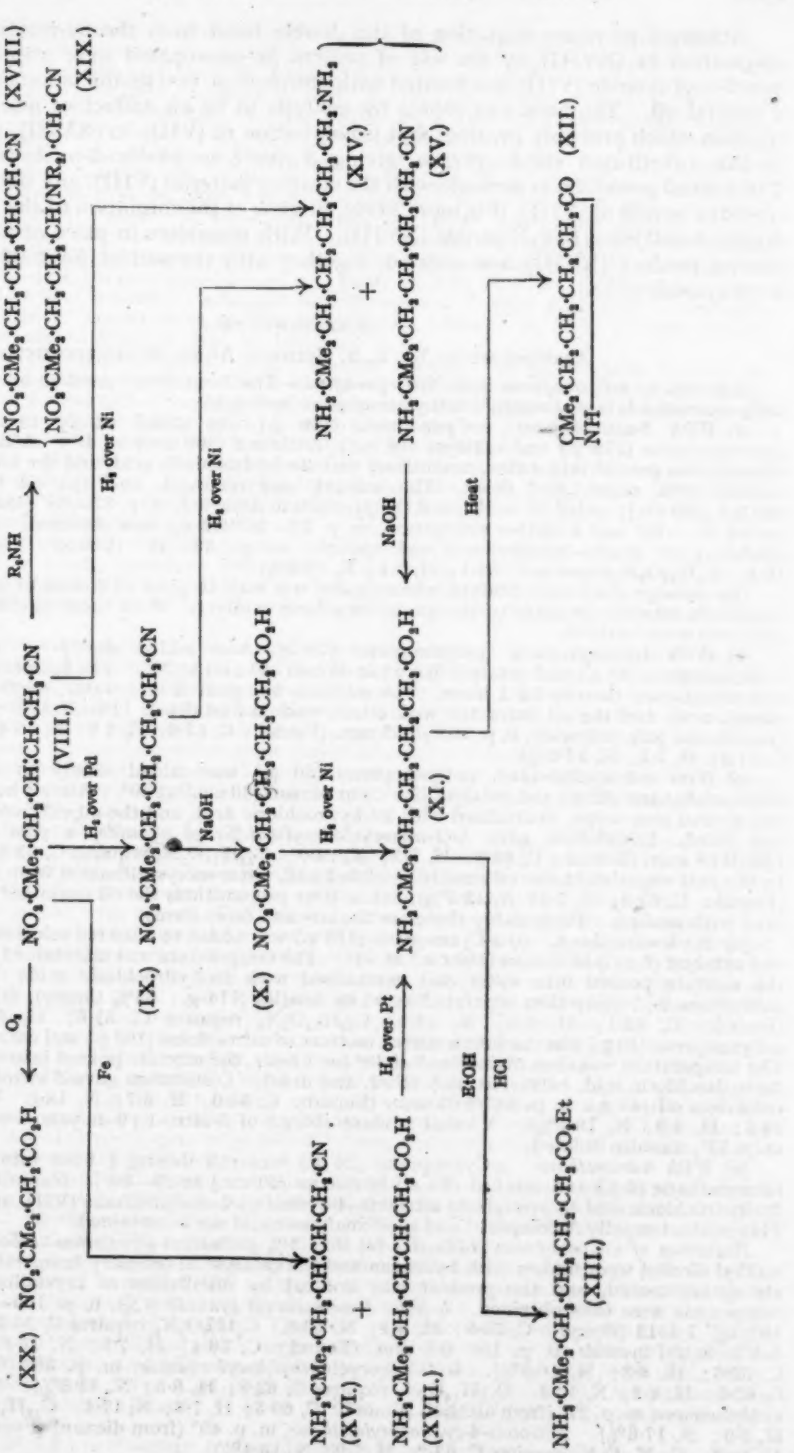
$NO_2{\cdot}CMe(CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CN)_2$ (VI.) $\qquad$ $NO_2{\cdot}C(CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CN)_3$ (VII.)

Hydrogenation of the adducts over Raney nickel generally proved unsatisfactory, reduction of the ethylene linkage being accompanied by varying amounts of reduction of the cyanide groups to amine. In all cases, however, the double bonds alone were reduced by using 5% palladium on calcium carbonate as catalyst: further reduction of the cyanide groups could then be effected over Raney nickel.

The reactions of the adducts have been studied chiefly with those derived from the two readily accessible nitro-paraffins, nitroethane and 2-nitropropane. The bis-adduct from nitroethane (VI) was hydrogenated over palladium on calcium carbonate to *5-nitro*-1 : 9-*dicyano*-*5-methylnonane*, which was hydrolysed to the corresponding *di-acid* and hydrogenated over Raney nickel to 1 : 6 : 11-*triamino*-*6-methylundecane*. Similarly, the 2-nitropropane adduct (VIII) was hydrogenated over palladium on calcium carbonate to *5-nitro-5-methylhexyl cyanide* (IX). Hydrolysis gave the *nitro-acid* (X), and this was reduced over Raney nickel to *5-amino-5-methylhexane*-1-*carboxylic acid* (XI) which, on being heated at 260°, gave the *lactam* (XII), and was esterified to the *ethyl* ester (XIII). Hydrogenation of the adduct (VIII) over Raney nickel gave a mixture of 1 : 6-*diamino*-*6-methylheptane* (XIV) [which was also obtained by similar reduction of the saturated nitro-cyanide (IX)] and *5-amino-5-methylhexyl cyanide* (XV) which was hydrolysed to the *amino-acid* (XI) previously obtained by reduction of the nitro-acid (X).

Reduction of 5-nitro-5-methylhex-2-enyl cyanide (VIII) with iron gave three products, (*a*) *5-amino-5-methylhex-2-enyl cyanide* (XVI), (*b*) *5-amino-5-methylhex-2-ene*-1-*carboxylic acid* (XVII) [identified by reduction over platinum to the saturated amino-acid (XI)], and (*c*) a base isomeric with the unsaturated amino-cyanide. The last has not been examined, but presumably either has the double bond αβ to the cyano-group or is the cyclised form of this, *i.e.*, 2-cyano-6 : 6-dimethylpiperidine.

Reactions of 5-nitro-5-methylhex-2-enyl cyanide.



Attempts to cause migration of the double bond from the βγ-position in (VIII) to the αβ-position in (XVIII) by the use of sodium in *iso*propanol were unsuccessful. When the hex-2-enyl cyanide (VIII) was treated with morpholine, two products were obtained, a base and a neutral oil. The base was shown by analysis to be an adduct of morpholine to (VIII), a reaction which probably involves first isomerisation of (VIII) to (XVIII), followed by addition to this substituted vinyl cyanide, giving *5-nitro-2-morpholino-5-methylhexyl cyanide* (XIX). The neutral product was isomeric with the starting material (VIII), and though it is possibly the *cis–trans* isomer of (VIII), it is more likely, in view of the formation of the adduct (XIX), to be *5-nitro-5-methylhex-1-enyl cyanide* (XVIII). With piperidine in place of morpholine, the same neutral product (XVIII) was isolated, together with the adduct *5-nitro-2-piperidino-5-methylhexyl cyanide* (XIX).

Experimental.

Analyses are by Mr. E. S. Morton. All m. ps. are uncorrected.

Reactions of α-Cyanoprene with Nitro-paraffins.—The " catalyst " used in all these additions was a 38% aqueous solution of methyltriethylammonium hydroxide.

(a) *With 2-nitropropane.* α-Cyanoprene (158 g.) was added slowly to a stirred solution of 2-nitropropane (178 g.) and catalyst (10 c.c.) in dioxan (200 c.c.) at 40°. After 2 hours at 40°, the mixture was poured into water, neutralised with 2N-hydrochloric acid, and the oil extracted with ether, washed with water, and dried. The solvent was removed, and the oil (300 g.) dissolved in alcohol (300 c.c.), cooled to − 10°, and the precipitate collected, m. p. 37—38° (135 g.). The filtrate was cooled to − 60° and a further precipitate, m. p. 32—38° (45 g.), was obtained. Recrystallisation from alcohol gave *5-nitro-5-methylhex-2-enyl cyanide*, m. p. 38—39° (Found: C, 56·8; H, 7·2; N, 16·4. $C_8H_{12}O_2N_2$ requires C, 57·1; H, 7·1; N, 16·6%).

The same product was obtained when alcohol was used in place of dioxan or with sodium hydroxide or sodium ethoxide in place of the quaternary base catalyst. With these modifications, however, the yield was more variable.

(b) *With 1-nitropropane.* α-Cyanoprene (79 g.) was added slowly to a stirred solution of 1-nitropropane (45 g.) and catalyst (5 c.c.) in dioxan (50 c.c.) at 35°. The temperature was raised to 40° and maintained thereat for 1 hour. The mixture was poured into water, neutralised with 2N-hydrochloric acid, and the oil extracted with ether, washed and dried. Distillation gave *5-nitrohept-2-enyl cyanide* as a pale yellow oil, b. p. 102°/0·07 mm. (Found: C, 57·6; H, 6·9; N, 16·4. $C_8H_{13}O_2N_2$ requires C, 57·2; H, 7·1; N, 16·6%).

(c) *With nitrocyclohexane.* α-Cyanoprene (20 g.) was added slowly to a stirred solution of nitrocyclohexane (32 g.) and catalyst (3 c.c.) in dioxan (30 c.c.) at 40°. After 1 hour at 40°, the mixture was poured into water, neutralised with 2N-hydrochloric acid, and the oil extracted with ether, washed, and dried. Distillation gave *4-(1-nitrocyclohexyl)but-2-enyl cyanide*, a pale yellow liquid, b. p. 142°/0·08 mm. (Found: C, 63·3; H, 7·7; N, 14·0. $C_{11}H_{16}O_2N_2$ requires C, 63·5; H, 7·7; N, 13·5%). In the first experiment the oil readily solidified and, after recrystallisation from alcohol, had m. p. 30° (Found: C, 63·3; H, 7·4; N, 13·5%), but in later preparations the oil could not be induced to solidify even with seeding. Presumably these are the *cis-* and *trans*-forms.

(d) *With nitroethane.* (i) α-Cyanoprene (119 g.) was added to a stirred solution of nitroethane (56 g.) and catalyst (6 c.c.) in dioxan (100 c.c.) at 30°. The temperature was maintained at 40° for 2 hours, and the mixture poured into water and neutralised with 2N-hydrochloric acid; *5-nitro-1:9-dicyano-5-methylnona-2:7-diene* then separated as white needles (114 g.; 65% theory), m. p. 77° (from alcohol) (Found: C, 62·1; H, 6·5; N, 18·1. $C_{12}H_{16}O_2N_2$ requires C, 61·8; H, 6·4; N, 18·0%). (ii) α-Cyanoprene (40 g.) was run into a stirred mixture of nitroethane (160 g.) and catalyst (6 c.c.) at 25—30°. The temperature was then maintained at 40° for 1 hour, the mixture poured into water, neutralised with 2N-hydrochloric acid, extracted with ether, and dried. Distillation gave *5-nitrohex-2-enyl cyanide* as a colourless oil (45 g.), b. p. 88°/0·05 mm. (Found: C, 54·0; H, 6·7; N, 18·1. $C_7H_{10}O_2N_2$ requires C, 54·5; H, 6·9; N, 18·1%). A small amount (10 g.) of 5-nitro-1:9-dicyano-5-methylnona-2:7-diene, m. p. 77°, was also isolated.

(e) *With nitromethane.* α-Cyanoprene (24 g.) was run during ½ hour into a stirred solution of nitromethane (6 g.) and catalyst (3 c.c.) in dioxan (50 c.c.) at 25—30°. The mixture was diluted with 2N-hydrochloric acid to precipitate nitrotris-(4-cyanobut-2-enyl)methane (VII), m. p. 72° (from dioxan). This product rapidly decomposed and good analyses could not be obtained.

Reduction of α-Cyanoprene Adducts.—(a) *Over 5% palladium on calcium carbonate.* The adducts in methyl alcohol were shaken with hydrogen and the catalyst at ordinary temperature and pressure until absorption ceased, and the product was isolated by distillation or crystallisation. The following compounds were thus obtained. *5-Nitro-5-methylhexyl cyanide* (IX), b. p. 100—102°/0·09 mm., m. p. 10°, $n_D^{19°}$ 1·4513 (Found: C, 56·9; H, 8·1; N, 16·8. $C_8H_{14}O_2N_2$ requires C, 56·5; H, 8·3; N, 16·5%). *5-Nitroheptyl cyanide*, b. p. 100°/0·1 mm. (Found: C, 56·4; H, 7·9; N, 16·8. $C_8H_{14}O_2N_2$ requires C, 56·5; H, 8·3; N, 16·5%). *4-(1-Nitrocyclohexyl)butyl cyanide*, m. p. 36° (from alcohol) (Found: C, 62·7; H, 8·2; N, 13·4. $C_{11}H_{18}O_2N_2$ requires C, 62·8; H, 8·5; N, 13·3%). *5-Nitro-1:9-dicyano-5-methylnonane*, m. p. 27° (from alcohol) (Found: C, 60·5; H, 7·8; N, 17·4. $C_{12}H_{18}O_2N_2$ requires C, 60·7; H, 8·0; N, 17·6%). *Nitrotris-4-cyanobutylmethane*, m. p. 49° (from dioxan) (Found: C, 63·1; H, 8·0; N, 18·2. $C_{16}H_{24}O_2N_4$ requires C, 63·2; H, 7·9; N, 18·4%).

(b) *With Raney nickel.* The adducts in methyl alcohol were reduced over Raney nickel at ordinary temperature and pressure and the products isolated by fractional distillation. 5-Nitro-5-methylhex-2-enyl cyanide gave: (i) *5-Amino-5-methylhexyl cyanide* (XV), b. p. 53—55°/0·06 mm. (Found: C, 68·8; H, 11·6; N, 19·7; equiv., 139·1. $C_8H_{16}N_2$ requires C, 68·6; H, 11·4; N, 20·0%; equiv., 140); *picrate*,

m. p. 130—131° (from water) (Found : C, 45·4; H, 5·35. $C_8H_{16}N_2,C_6H_3O_7N_3$ requires C, 45·5; H, 5·2%); *benzoyl* derivative, m. p. 94—95° (from *cyclo*hexane) (Found : N, 11·2. $C_{15}H_{20}ON_2$ requires N, 11·5%); 2 : 4-*dinitrophenylurea* (cf. McVeigh and Rose, *J.*, 1945, 621), m. p. 163—164° (from alcohol) (Found : C, 52·0; H, 5·1; N, 19·8. $C_{15}H_{19}O_5N_5$ requires C, 51·6; H, 5·4; N, 20·0%). (ii) 1 : 6-Diamino-6-methylheptane (XIV), b. p. 36—37°/0·12 mm.; *dihydrochloride*, m. p. 195—196° (from alcohol–acetone) (Found : Cl, 32·5. $C_8H_{20}N_2,2HCl$ requires Cl, 32·7%); *dibenzoyl* derivative, m. p. 162—163° (from alcohol) (Found : C, 75·2; H, 8·0; N, 8·5. $C_{22}H_{28}O_2N_2$ requires C, 75·0; H, 8·0; N, 8·0%); *dipicrate*, m. p. 212° (decomp.) (from alcohol) (Found : C, 40·05; H, 4·45. $C_8H_{20}N_2,2C_6H_3O_7N_3$ requires C, 39·9; H, 4·3%). 5-Nitrohept-2-enyl cyanide gave 1 : 6-diamino-octane, b. p. 100°/0·08 mm.; *dipicrate*, m. p. 158—160° (from water) (Found : C, 40·15; H, 4·65; N, 18·75. $C_8H_{20}N_2,2C_6H_3O_7N_3$ requires C, 39·9; H, 4·3; N, 18·6%). 4-(1-Nitro*cyclo*hexyl)but-2-enyl cyanide (both forms) gave 5-(1-amino-*cyclo*hexyl)amylamine, b. p. 147°/15 mm.; *mono*-2 : 4-*dinitrophenylurea* derivative (cf. McVeigh and Rose, *loc. cit.*), m. p. 138—140° (from xylene) (Found : C, 54·9; H, 7·0; N, 17·9. $C_{15}H_{27}O_5N_5$ requires C, 54·9; H, 6·8; N, 17·8%). 5-Nitro-1 : 9-dicyano-5-methylnona-2 : 7-diene gave 1 : 6 : 11-triamino-undecane, b. p. 131°/0·1 mm.; *tripicrate*, m. p. 125° (from water) (Found : C, 39·9; H, 4·2; N, 18·5. $C_{12}H_{32}N_3,3C_6H_3O_7N_3$ requires C, 39·9; H, 4·2; N, 18·6%).

(c) *With iron.* Iron dust (30—60 mesh; 25 g.) in water (50 c.c.) was treated with 35% hydrochloric acid (10 c.c.) and stirred at 90° until no longer acid to Congo-red. 5-Nitro-5-methylhex-2-enyl cyanide (VIII) (20 g.) was added during ½ hour and the temperature maintained at 95° for a total of 4½ hours. The product was cooled, filtered, and evaporated to dryness at 60°/16 mm. Addition of acetone to the gum gave a crystalline solid which, after recrystallisation from acetone, gave a hydrochloride, m. p. 163—164°, from which the *picrate*, m. p. 121—123° (decomp.) (from water), was formed (Found : C, 45·95; H, 4·75. $C_8H_{14}N_2,C_6H_3O_7N_3$ requires C, 45·8; H, 4·6%); *benzoyl* derivative, m. p. 59—60° (from water) (Found : C, 74·35; H, 7·4. $C_{15}H_{18}ON_2$ requires C, 74·4; H, 7·4%). This base is probably 2-cyano-6 : 6-dimethylpiperidine.

The original acetone filtrate was evaporated to dryness, dissolved in excess of aqueous sodium hydroxide, and repeatedly extracted with ether. The ethereal solution was dried and distilled to give 5-amino-5-methylhex-2-enyl cyanide (1·4 g.; 9%), b. p. 49—51°/0·15 mm.; *picrate*, m. p. 175—176° (from water) (Found : C, 45·65; H, 4·4; N, 19·1. $C_8H_{14}N_2,C_6H_3O_7N_3$ requires C, 45·8; H, 4·6; N, 19·1%).

The aqueous layer after ether extraction was acidified with hydrochloric acid, evaporated to dryness, extracted with concentrated hydrochloric acid, and the sodium chloride separated. The filtrate was again evaporated to dryness, treated with excess of silver oxide in water, filtered, and the solution of silver salt saturated with hydrogen sulphide and filtered. The filtrate was evaporated to dryness, giving 5-amino-5-methylhexene-1-carboxylic acid (2·6 g.), partly purified by dissolving in water and precipitating with acetone : the decomposition point varied between 210° and 230° according to the rate of heating. Good analytical figures for the acid were not obtained, but hydrogenation in water over Adams's platinum gave 5-amino-5-methylhexane-1-carboxylic acid (XI), m. p. and mixed m. p. with authentic specimen 256—258° (decomp.).

Reactions with 5-Nitro-5-methylhex-2-enyl Cyanide.—(a) *Ozonisation.* The nitro-cyanide (10 g.) in alcohol (30 c.c.) was treated with excess of ozonised oxygen and run slowly into a mixture of 10% hydrogen peroxide (36 c.c.) containing sulphuric acid (0·56 c.c.). The mixture was heated to 86° during 1 hour and refluxed at that temperature for 2 hours. After cooling, water (50 c.c.) was added and the mixture thoroughly extracted with ether. The ethereal extract was washed with aqueous sodium carbonate, and the alkaline extract acidified and evaporated to dryness. The solid residue was extracted with ether; on removal of the ether a solid (1·9 g.) was obtained which was recrystallised from water (with considerable loss) and from *cyclo*hexane to give 2-nitro*iso*valeric acid (XX), m. p. 104—105° (Found : C, 40·65; H, 6·15; N, 9·3; equiv., 146·0. Calc. for $C_5H_9O_4N$: C, 40·8; H, 6·1; N, 9·5%; equiv., 147·0).

(b) *Action of morpholine.* The nitro-cyanide (10 g.) in morpholine (20 c.c.) was kept for 7 days, then warmed to 40° for 3 hours, cooled, poured into water, and acidified with hydrochloric acid to Congo-red. By ether-extraction, a neutral product, *5-nitro-5-methylhex-1-enyl cyanide* (XVIII), b. p. 102—108°/0·1 mm., $n_D^{18°}$ 1·4716, was obtained (Found : C, 57·5; H, 6·9; N, 17·1. $C_8H_{12}O_2N_2$ requires C, 57·2; H, 7·1; N, 16·7%). This did not solidify on being seeded with the starting material. The aqueous layer was basified, and a base, *5-nitro-2-morpholino-5-methylhexyl cyanide* (XIX), isolated by ether extraction; b. p. 148—151°/0·08 mm., m. p. 36—37° (from *cyclo*hexane) (Found : C, 56·3; H, 8·1; N, 16·1. $C_{12}H_{21}O_3N_3$ requires C, 56·5; H, 8·2; N, 16·5%).

(c) *Action of piperidine.* A similar experiment using piperidine (20 c.c.) in place of morpholine gave 5-nitro-5-methylhex-1-enyl cyanide (XVIII), b. p. 96—98°/0·05 mm., $n_D^{20°}$ 1·4702 (Found : C, 57·1; H, 7·2%), and *5-nitro-2-piperidino-5-methylhexyl cyanide* (XIX), b. p. 134—136°/0·25 mm. (Found : C, 61·95; H, 8·9; N, 16·7. $C_{13}H_{23}O_2N_3$ requires C, 61·7; H, 9·1; N, 16·6%).

Miscellaneous Reactions.—(a) *Hydrolysis and hydrogenation of 5-nitro-5-methylhexyl cyanide* (IX). The cyanide (84 g.) was refluxed in alcohol (280 c.c.) with 32% aqueous sodium hydroxide (60 c.c.) for 10 hours, excess of alkali removed with 35% hydrochloric acid (15 c.c.), and the solution, after clarification with carbon, evaporated to dryness. The solid was dissolved in water (200 c.c.), clarified with carbon, and the acid precipitated with hydrochloric acid; m. p. 45—48° (91 g.). The *5-nitro-5-methylhexane-1-carboxylic acid* (X) was purified by distillation, b. p. 116°/0·08 mm., m. p. 47—48° (Found : N, 7·45; equiv., 191. $C_8H_{15}O_4N$ requires N, 7·4%; equiv., 189); *benzylthiuronium* salt, m. p. 168—169° (from alcohol) (Found : C, 53·6; H, 7·15. $C_8H_{15}O_4N,C_8H_{10}N_2S$ requires, C, 54·1; H, 7·0%).

This nitro-acid (X) (57·5 g.) in N-sodium hydroxide (308 c.c.) was hydrogenated over Raney nickel. The product was filtered, strongly acidified with hydrochloric acid, evaporated to dryness, and the amino-acid hydrochloride extracted from sodium chloride with 35% hydrochloric acid (100 c.c.). [A sample of the *hydrochloride* was crystallised from alcohol–ether; m. p. 172—174° (decomp.) (Found : N, 6·95; Cl, 17·9. $C_8H_{17}O_2N,HCl$ requires N, 7·2; Cl, 18·2%).] The hydrochloride in water was heated

at 70° with excess of silver oxide, and the hot solution filtered and saturated with hydrogen sulphide. The silver sulphide was separated and the aqueous solution evaporated to dryness. The residue was dissolved in water and treated with acetone to precipitate *5-amino-5-methylhexane-1-carboxylic acid* (XI), m. p. 259—261° (decomp.) (34 g.) (Found: C, 60·4; H, 10·8; N, 9·2. $C_8H_{17}O_2N$ requires C, 60·4; H, 10·7; N, 8·8%). The *ethyl* ester (XIII), prepared by heating the acid with hydrogen chloride in alcohol, had b. p. 120°/19 mm. (Found: C, 64·0; H, 11·2. $C_{10}H_{21}O_2N$ requires C, 64·2; H, 11·2%). The acid (XI) was heated at 280° for ½ hour and the residue distilled to give the *lactam* (XII), b. p. 135°/13 mm., m. p. 102—103° (from ligroin) (Found: C, 67·7; H, 10·5; N, 9·85. $C_8H_{15}ON$ requires C, 68·1; H, 10·6; N, 9·9%).

(b) *Hydrolysis of 5-amino-5-methylhexyl cyanide* (XV). The cyanide (7·1 g.) was refluxed in alcohol (35 c.c.) with 32% aqueous sodium hydroxide (7·1 c.c.) for 16 hours. The mixture was acidified with hydrochloric acid, evaporated to dryness, and the 5-amino-5-methylhexane-1-carboxylic acid (XI) isolated as in (a); m. p. 256—259° (decomp.), mixed m. p. with acid prepared as in (a), 257—259° (decomp.).

(c) *Hydrolysis of 5-nitro-1 : 9-dicyano-5-methylnonane.* The dicyano-compound (100 g.) was refluxed for 20 hours in alcohol (400 c.c.) with 32% aqueous sodium hydroxide (120 c.c.). Excess of alkali was neutralised with hydrochloric acid, the solution clarified with carbon and filtered, and the acid precipitated by addition of excess of hydrochloric acid and crystallised from water to give *5-nitro-5-methylnonane-1 : 9-dicarboxylic acid*, m. p. 75—76° (Found: C, 52·55; H, 7·65; N, 5·5. $C_{12}H_{21}O_6N$ requires C, 52·4; H, 7·6; N, 5·1%), *bisbenzylthiuronium* salt, m. p. 151—152° (from methyl alcohol–acetone) (Found: N, 11·6. $C_{12}H_{21}O_6N,2C_8H_{10}N_2S$ requires N, 11·5%).

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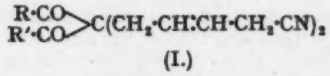
58. *Reactions of α-Cyanoprene (1-Cyanobuta-1 : 3-diene). Part II. Addition of Reactive Methylene Compounds.*

By (MRS.) J. L. CHARLISH, W. H. DAVIES, and J. D. ROSE.

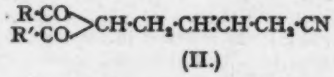
Ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, and acetylacetone add to α-cyanoprene (1-cyanobuta-1 : 3-diene) to give products of the type $CXY(CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CN)_2$. On being heated, these lose one mol. of α-cyanoprene yielding $CHXY{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CN$. Both types of compound are hydrogenated to saturated cyanides over 5% palladium on calcium carbonate. Certain other active methylene compounds do not add to α-cyanoprene.

IN Part I (previous paper), the addition of nitro-paraffins to α-cyanoprene (1-cyanobuta-1 : 3-diene) was described. Extending this work, ethyl malonate, ethyl acetoacetate, ethyl cyanoacetate, and acetylacetone have now been added to α-cyanoprene in the presence of methyltriethylammonium hydroxide as catalyst. In each case, the main product was the adduct of two mols. of α-cyanoprene to one mol. of active methylene compound. The adducts were thermally unstable and lost a mol. of α-cyanoprene on being heated. Hydrogenation of the bis-adducts over Raney nickel caused partial reduction of the cyano-groups, but by using 5% palladium on calcium carbonate as catalyst the double bonds were reduced smoothly, without attack on the ketonic or cyano-groups.

In the reaction with ethyl malonate, the bis-addition product, *ethyl 1 : 9-dicyanonona-2 : 7-diene-5 : 5-dicarboxylate* (I; R = R′ = OEt), was isolated in only poor yield (13%) owing to its high solubility in common solvents and its thermal instability. When heated to 200°, the adduct split off α-cyanoprene to give *ethyl 1-cyanopent-2-ene-5 : 5-dicarboxylate* (II; R = R′ = OEt) which after hydrogenation, hydrolysis, and decarboxylation gave pimelic acid (IV) thus establishing that addition to α-cyanoprene had been 1 : 4 and not 1 : 2, as 1 : 2-addition followed by this series of reactions would have yielded β-ethylglutaric acid.



(I.)



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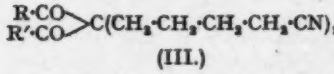

(III.)

$CO_2H{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$

(IV.)

In the reaction with acetylacetone, the bis-adduct, *1 : 9-dicyano-5 : 5-diacetylnona-2 : 7-diene* (I; R = R′ = Me), was isolated in two forms which gave on reduction the same tetrahydro-derivative (III; R = R′ = Me). It is thought that the two forms are probably *cis–trans* isomers. By heating the adduct, α-cyanoprene was eliminated; the resulting 5 : 5-diacetylpent-2-enyl cyanide (I; R = R′ = Me), which could not be purified, was reduced and hydrolysed

to give 5-acetylhexoic acid, m. p. 27—29° (lit. m. p. 29—30°); semicarbazone, m. p. 113—114° (lit. m. p. 113°). This confirms that acetylacetone also adds to α-cyanoprene in the 1 : 4-position.

Ethyl acetoacetate added to α-cyanoprene in a similar fashion to give a bis-adduct, *ethyl* 1 : 9-*dicyano*-5-*acetylnona*-2 : 7-*diene*-5-*carboxylate* (I; R = Me, R′ = OEt), which was hydrogenated over palladium on calcium carbonate to *ethyl* 1 : 9-*dicyano*-5-*acetylnonane*-5-*carboxylate* (II; R′ = Me, R = OEt).

The adduct from ethyl cyanoacetate could not be purified, but after hydrogenation over palladium on calcium carbonate, the tetrahydro-derivative *ethyl* 1 : 5 : 9-*tricyanononane*-5-*carboxylate* was obtained.

It would appear that, for addition to α-cyanoprene to occur, it is necessary to have a fairly highly activated methylene group. Attempts to carry out addition with benzyl cyanide, deoxybenzoin, and acetophenone were unsuccessful or gave very small yields; with *cyclo*pentadiene, only tars were formed.

Experimental.

The " catalyst " used in these experiments was a 38% aqueous solution of triethylmethylammonium hydroxide.

Ethyl Malonate Reactions.—(a) *Ethyl* 1 : 9-*dicyanonona*-2 : 7-*diene*-5 : 5-*dicarboxylate* (I; R = R′ = OEt). α-Cyanoprene (53·4 c.c., 0·6 mol.) was run slowly into a stirred solution of ethyl malonate (45 c.c., 0·3 mol.) and catalyst (2·0 c.c.) in dioxan (60 c.c.) at 40° ± 2°. The mixture was maintained at 40° for 2 hours, poured into water, and extracted with ether. The ethereal solution was dried, and low-boiling material (below b. p. 49°/0·07 mm.) removed. The residual oil (37 g.) was dissolved in ether (50 c.c.), filtered, and cooled to − 60° to give the white crystalline *dicyano*-compound (m. p. 44—48°; 9·1 g.) which after further crystallisation from alcohol had m. p. 49—50° (Found: C, 64·1; H, 6·5; N, 9·4. $C_{17}H_{22}O_4N_2$ requires C, 64·2; H, 6·9; N, 8·8%).

(b) *Ethyl* 1-*cyanopent*-2-*ene*-5 : 5-*dicarboxylate* (II; R = R′ = OEt). The solvent was removed from the ethereal mother liquors of the dicyano-compound (previous section), and the residue, after 2 hours' heating at 200°/15 mm., was distilled to give a colourless oil, b. p. 194—198°/14 mm., refractionated to b. p. 196—198°/14 mm. (16·5 g.) (Found: C, 60·1; H, 7·0. $C_{12}H_{17}O_4N$ requires C, 60·3; H, 7·1%).

(c) *Ethyl* 1 : 9-*dicyanononane*-5 : 5-*dicarboxylate* (III; R = R′ = OEt). The unsaturated dicyano-derivative (I; R = R′ = OEt) (2 g.) in alcohol (80 c.c.) was hydrogenated at ordinary temperature and pressure over 5% palladium on calcium carbonate (0·1 g.). After filtration, the solvent was removed and the residual solid crystallised from ether with ice-cooling to give *ethyl* 1 : 9-*dicyanononane*-5 : 5-*dicarboxylate*, m. p. 50—51° (mixed m. p. with starting material, 33—38°) (Found: C, 63·7; H, 8·0; N, 8·9. $C_{17}H_{26}O_4N_2$ requires C, 63·4; H, 8·1; N, 8·7%).

(d) *Pimelic acid* (IV). Ethyl 1-cyanopent-2-ene-5 : 5-dicarboxylate (12 g.) in alcohol (60 c.c.) was hydrogenated at ordinary temperature and pressure over 5% palladium on calcium carbonate (0·5 g.). The product was filtered and the solvent removed. As attempted distillation at 0·05 mm. caused decomposition, the crude oil (12 g.) was refluxed for 8 hours with 20% aqueous sodium hydroxide (40 c.c.), cooled, acidified with hydrochloric acid, treated with carbon, filtered, and the filtrate evaporated to dryness. The residual tricarboxylic acid was extracted from the sodium chloride with ether, the solvent removed, and the crude tri-acid (9·0 g.) heated at 135—140° for 1 hour and then at 165° for 15 minutes. The product (6·6 g.) solidified on cooling and was crystallised successively from benzene and water to m. p. 103—104°, not depressed by admixture with an authentic specimen of pimelic acid, m. p. 103° (Found: C, 52·8; H, 7·1; equiv., 81·5. Calc. for $C_7H_{12}O_4$: C, 52·5; H, 7·5%; equiv., 80·0).

Acetylacetone Reactions.—(a) 1 : 9-*Dicyano*-5 : 5-*diacetylnona*-2 : 7-*diene* (I; R = R′ = Me). α-Cyanoprene (71·2 c.c., 0·8 mol.) was run into a stirred solution of acetylacetone (39 c.c., 0·4 mol.) and catalyst (6 c.c.) in dioxan (80 c.c.) at 35—40°. The temperature was maintained at 40° for 1 hour, then raised to 70° and kept there for 1 hour. After cooling, the mixture was diluted with ether (100 c.c.) and cooled in ice to give a crystalline *product*, m. p. 86—89° (46 g.), which after recrystallisation from alcohol had m. p. 88—89° (Found: C, 69·4; H, 6·9; N, 11·1. $C_{15}H_{18}O_2N_2$ requires C, 69·8; H, 7·0; N, 10·85%). The ethereal filtrate was washed well with water, dried, and the solvent removed. The residual oil was dissolved in alcohol (30 c.c.) and cooled in ice to give a solid *product*, m. p. 82—84°, which after repeated crystallisation from alcohol had m. p. 83—84° and gave no mixed m. p. depression with the previously isolated product, m. p. 88—89°, with which it was isomeric (Found: C, 70·1; H, 7·1; N, 10·7%).

In another experiment, the total reaction mixture was poured into water and treated with ether to give a crystalline precipitate, m. p. 79—83°, from which only the isomer, m. p. 83—84°, was isolated.

(b) 5-*Acetylhexoic acid.* 1 : 9-Dicyano-5 : 5-diacetylnona-2 : 7-diene (40 g.) was slowly distilled to give a low boiling fraction, b. p. <130°/17 mm. (5·2 g.), consisting mainly of α-cyanoprene, a fraction, b. p. 130—196°/17 mm. (29·5 g.), and a black residue (9·0 g.). Refractionation of the main product gave a yellow mobile oil, b. p. 180—200°/17·5 mm. (18·6 g.), which was obviously a mixture. This was hydrogenated in methyl alcohol (100 c.c.) over 5% palladium on calcium carbonate (0·5 g.), filtered, and the solvent removed. As this oil (mainly 5 : 5-diacetylhexoic acid) appeared to decompose on distillation, it was hydrolysed by refluxing it for 6 hours with 10% sodium hydroxide (70 c.c.). The acid was isolated by acidification, extraction with ether, and distillation to give an oil, b. p. 105—115°/0·1 mm. (3·7 g.). Refractionation gave a small amount of 5-acetylhexoic acid, b. p. 180—181°/17 mm., m. p. 27—29°. [Léser (*Compt. rend.*, 1905, **141**, 1032) gives b. p. 184—185°/20 mm., m. p. 30°; Kipping and Perkin (*J.*, 1889, **55**, 338) report that 5-acetylhexoic acid when very impure is almost entirely decomposed when distilled under reduced pressure.] The keto-acid gave a *semicarbazone* containing acetic acid of crystallisation, m. p. 113—114·5° (from aqueous acetic acid) [Wallach (*Annalen*, 1906, **345**, 141) gives

m. p. 113—114° but does not record an analysis] (Found: C, 47·8; H, 7·8; N, 15·4. $C_9H_{17}O_3N_3,C_2H_4O_2$ requires C, 48·0; H, 7·6; N, 15·3%), and a 2 : 4-*dinitrophenylhydrazone*, m. p. 120—121° (Found: N, 16·6. $C_{14}H_{18}O_6N_4$ requires N, 16·6%).

(c) 1 : 9-*Dicyano-5-diacetylnonane* (III; R = R′ = Me). 1 : 9-Dicyano-5 : 5-diacetylnona-2 : 7-diene (2 g.) in methyl alcohol (150 c.c.) was hydrogenated in the same way as the dicarbethoxy-derivative (c, p. 233) to give 1 : 9-*dicyano-5* : 5-*diacetylnonane*, m. p. 90—91° (from alcohol) (Found: C, 68·5; H, 8·1; N, 10·8. $C_{15}H_{22}O_2N_2$ requires C, 68·7; H, 8·4; N, 10·7%). The two forms of the unsaturated dicyanide gave the same saturated product on hydrogenation.

Ethyl Acetoacetate Reactions.—(a) *Ethyl* 1 : 9-*dicyano-5-acetylnona-2* : 7-*diene-5-carboxylate* (I; R = Me, R′ = OEt). α-Cyanoprene (35·6 c.c., 0·4 mol.) was run into a stirred solution of ethyl acetoacetate (25·4 c.c., 0·2 mol.) and catalyst (2 c.c.) in dioxan (40 c.c.) at 35—40°. After being maintained at 40° for 2 hours the mixture was poured into water, and the oil was separated and dissolved in alcohol (40 c.c.). On cooling to 0° the *dicyano*-derivative separated (m. p. 73—75°; 32·2 g.) and was recrystallised from alcohol; m. p. 75—76° (Found: C, 66·7; H, 6·9; N, 10·3. $C_{16}H_{20}O_3N_2$ requires C, 66·7; H, 6·9; N, 9·95%).

(b) *Ethyl* 1 : 9-*dicyano-5-acetylnonane-5-carboxylate* (III; R = Me, R′ = OEt). The unsaturated dicyano-compound (2 g.) was hydrogenated in the same way as the dicarbethoxy-derivative (c, p. 233) to give *ethyl* 1 : 9-*dicyano-5-acetylnonane-5-carboxylate*, m. p. 85—86° (from alcohol) (mixed m. p. with unsaturated dicyano-compound, 69—73°) (Found: C, 65·5; H, 7·95; N, 9·8. $C_{16}H_{24}O_3N_2$ requires C, 65·75; H, 8·2; N, 9·6%).

Ethyl Cyanoacetate Reactions.—*Ethyl* 1 : 5 : 9-*tricyanononane-5-carboxylate*. α-Cyanoprene (26·7 c.c.) was run into a stirred solution of ethyl cyanoacetate (16 c.c.) and catalyst (1 c.c.) in dioxan (30 c.c.) at 40°. The temperature was raised to 65° and kept there for 1 hour. The product was poured into water, extracted with ether, and the extract washed with dilute sulphuric acid. The resulting orange oil could not be obtained solid and decomposed on attempted distillation at 0·1 mm. The crude product in dioxan (100 c.c.) was hydrogenated over 6% palladium on calcium carbonate (1 g.), filtered, the solvent removed, and the residual oil (31·6 g.) repeatedly crystallised from alcohol at 0° to give the saturated *tricyano*-compound (25 g., 60%), m. p. 45—47° (Found: C, 65·1; H, 7·5; N, 15·0. $C_{15}H_{21}O_2N_3$ requires C, 65·45; H, 7·6; N, 15·3%).

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59. *The Spontaneous Low-temperature Polymerisation of Acetaldehyde.*

By H. A. RIGBY, C. J. DANBY, and C. N. HINSHELWOOD.

The spontaneous low-temperature polymerisation of acetaldehyde is shown by quantitative measurements at various temperatures to occur only in the act of crystallisation, and to yield a product containing a small number of long chains. The reaction whereby these grow is strongly inhibited by the addition of other organic liquids to the aldehyde. The polymer appears to be a polyoxymethylene of variable character, some samples of which depolymerise rather readily at room temperature.

THE fact that acetaldehyde polymerises on cooling to low temperatures has been familiar for many years, but only qualitative experiments on the reaction have been reported. Travers (*Trans. Faraday Soc.*, 1936, **32**, 246) found that the reaction occurred more readily after successive vacuum distillations of the aldehyde, and concluded that it was inhibited by oxygen. Letort (*Compt. rend.*, 1936, **202**, 767; Letort and Duval, *ibid.*, 1943, **216**, 58, 606) obtained the polymer by condensation of the vapour at low pressures in a vessel cooled in liquid air. Under these conditions the reaction did not appear to be sensitive, at least qualitatively, to the purity of the material or to the presence of oxygen. By distilling off the unchanged aldehyde under reduced pressure the polymer was obtained as a colourless rubber-like material.* Both Travers and Letort found that depolymerisation took place readily, particularly above room temperature.

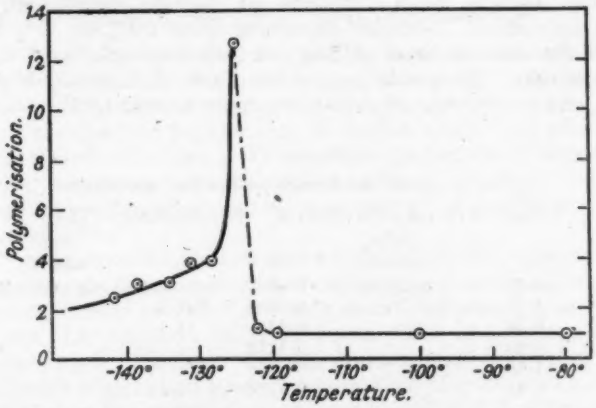
This polymerisation seemed to be a reaction of unusual interest in that it appeared to occur at a greater rate at a lower temperature. In the reaction of propylene with hydrogen chloride a similar behaviour has been attributed to an orientation effect (Sutherland and Maass, *Canadian J. Res.*, 1931, **5**, 48).

The present paper describes experiments on the kinetics of the low-temperature polymerisation of acetaldehyde which were carried out in order to throw light on the mechanism of the reaction. Experiments were also made to determine the probable nature of the polymer.

* *Added in Proof.*—Since this paper was written we have received the communication of Letort, Duval, and Rollin (*Compt. rend.*, 1947, **224**, 50) reporting the non-occurrence of the polymerisation above the freezing point.

Experimental Methods.—Acetaldehyde was carefully fractionated through a long column. Experiments were made on 10 c.c. samples contained in stoppered " Pyrex " test tubes. Cooling was effected by three different methods, (*a*) direct immersion in liquid nitrogen, (*b*) immersion in liquid oxygen (with a thin copper sleeve around the test-tube as a safety precaution), and (*c*) immersion in a simple cryostat. The cryostat consisted of a cylindrical Dewar vessel containing light petroleum which was stirred and maintained at the required temperature by means of liquid air syphoned at the appropriate rate from a storage vessel into a metal tube closed at the bottom and dipping into the cryostat. In this way temperatures between — 80° and — 140° could be maintained within about 1° for considerable periods. They were measured by a pentane thermometer calibrated against a copper–constantan thermocouple and potentiometer.

The relative extent of polymerisation in different experiments was estimated by measurements of viscosity at 0° in Ostwald viscometers, calibrated by the use of suitable glycerol–water mixtures. Polymer samples which were too viscous to flow in an ordinary viscometer were compared by measuring the viscosity of acetone solutions. A few experiments were made on very viscous specimens by determining the rate of fall of small steel balls in the liquid.



Effect of temperature on the polymerisation of acetaldehyde. (*The degree of polymerisation is given in terms of the viscosity of a standard acetone solution of the polymerised material relative to that of a corresponding solution of pure acetaldehyde.*)

Effect of Temperature.—A series of identical samples of aldehyde were cooled in the cryostat for periods of 10 minutes at different temperatures between — 80° and — 140°. The products were warmed rapidly to room temperature and dissolved in a standard volume of acetone, and the viscosity was measured. The results are given in the figure, where the viscosity of the solution (in terms of the time of flow relative to that of a corresponding solution of pure acetaldehyde) is plotted against temperature.

It will be seen that above the freezing point of acetaldehyde (— 123·5°) there is no polymerisation. Acetaldehyde cooled just to its freezing point polymerises to a considerable extent. Samples placed in a bath at still lower temperatures suffer progressively less polymerisation. Other experiments showed that samples which had been cooled to the freezing point but which did not solidify owing to super-cooling did not polymerise. From this it would appear that polymerisation takes place only when the acetaldehyde is in the act of crystallising at its freezing point. The polymerisation evidently decreases at lower temperature because the increasing rate of solidification leaves less time for polymerisation. This is confirmed by experiments in which the samples were cooled directly in a bath of liquid nitrogen. This gave very rapid freezing of the aldehyde and very little polymerisation was observed. Erratic results obtained with samples cooled in liquid oxygen and having a metal sleeve round the container are due to the irreproducible rates of cooling, as was shown by experiments in which the actual rate of fall in temperature was observed by a thermocouple placed in the tube.

Effect of Time of Cooling.—To investigate whether, at a fixed temperature, the reaction was progressive, or whether, as concluded above, it occurred only during the actual act of freezing, the following experiment was carried out. A series of identical samples of aldehyde were immersed simultaneously in the low-temperature bath and removed after different periods of time. Each sample of polymer was dissolved in fixed volumes of acetone, and the extent of polymerisation determined as explained above. The results are given in Table I, in which t is the time of cooling in minutes and η is the viscosity of the acetone solution relative to the standard. It will be seen that the reaction is not progressive, but appears only to occur during the initial act of freezing.

TABLE I.

Variation of the extent of polymerisation with time at a fixed temperature.

Temp.	*t.*	η.	Temp.	*t.*	η.	Temp.	*t.*	η.
−125°	10	7·07	−127°	10	2·09 *	−132°	10	3·27
	20	5·37		20	6·68		20	2·40
	30	5·56		30	6·79		30	2·37
	40	5·68		40	7·62		40	2·51

* Probably supercooled.

In a similar experiment the sample of aldehyde was cooled for a short time, allowed to warm to room temperature, tested, and then cooled again. All the increase in viscosity took place during the first period of cooling. No further reaction was observed during subsequent freezings.

Effect of Added Substances on the Polymerisation.—A series of experiments were made with aldehyde containing known small amounts of foreign substances, namely acetone, propaldehyde, and chloroform. Samples containing from 1·0% to 10% of these substances were prepared, and the relative times of flow after cooling for a fixed time under standard conditions were measured. The results are given in Table II, in which M is the molar fraction of added substance, and η is the viscosity relative to pure acetaldehyde.

TABLE II.

Effect of added substances on the polymerisation.

Time of cooling, 10 minutes. Temperature, −130°.

Subs. added.	*M.*	η.	Subs. added.	*M.*	η.	Subs. added.	*M.*	η.
Acetone	0·0076	46·25	Propaldehyde	0·0077	very large	Chloroform	0·0207	very large
	0·0151	5·20		0·0154	346·9		0·0340	205·3
	0·0225	2·78		0·0229	31·1		0·0470	15·9
	0·0298	4·68		0·0376	4·17		0·0596	6·3
	0·0365	1·50		0·0518	5·74		0·0779	2·4
	0·0440	1·49		0·0724	4·39			

It will be seen that quite small amounts of added substances reduce the extent of polymerisation to a marked extent. (The greatly reduced polymerisation observed with samples of acetaldehyde which had been stored after distillation may be attributed to traces of paraldehyde and acetic acid formed by slow polymerisation or oxidation. The different rates of polymerisation observed on different occasions and with different samples of aldehyde are to be attributed similarly to the presence of small amounts of impurity.)

The Depolymerisation.—The product obtained by cooling aldehyde under the conditions described was a very viscous liquid, or even a gel. Large quantities of unchanged aldehyde could be removed under reduced pressure leaving a rubber-like spongy solid. When kept at room temperature this reverted fairly rapidly to a liquid of which a considerable proportion was aldehyde. The rate of this depolymerisation varied considerably with different samples of polymer; the most stable remained solid for about two weeks: others became liquid in a few days.

The polymer was readily soluble in acetone, giving a viscous solution. Depolymerisation, as measured by the decrease in viscosity, took place at least as readily in solution as in the solid. A series of experiments were made in which the change of viscosity of acetone solutions of the polymer with time at different temperatures was measured. Again a very marked difference in the behaviour of different samples was encountered. It was not found possible to obtain a satisfactory temperature coefficient from which the activation energy of the depolymerisation might have been calculated. All the samples investigated appeared to be stable below a given temperature, and to depolymerise at an increasing rate at higher temperatures. The temperature below which depolymerisation did not take place varied from sample to sample, some being stable below − 9°, some only below − 20°.

The Nature of the Polymer.—(a) *Molecular weight.* The number average molecular weight of samples of acetaldehyde which had been polymerised so as to have a high viscosity was measured cryoscopically in benzene. Values in the region of 55 were obtained. The solution therefore consisted of a relatively small number of rather large polymer molecules dissolved in unchanged aldehyde. The fact that the material obtained by the removal of the aldehyde was an elastic solid indicated that its molecular weight was probably in the region of several thousand. This solid dissolved in benzene only very slowly. The resulting solutions gave molecular weights of the order of 600. This low value was clearly due to partial depolymerisation, or incomplete removal of residual unchanged acetaldehyde.

(b) X-*Ray diffraction investigation.* Several *X*-ray diffraction photographs of thin films of the solid polymer were taken by Mr. H. M. Powell, who found two diffuse rings of diameters 3·16 cm. and 1·65 cm. (copper $K\alpha$ radiation, film–specimen distance 3·8 cm.), corresponding to repeat distances of 3·9 A. and 7·2 A.

(c) *Chemical evidence.* Chemical analysis confirmed that the polymer had the same empirical formula as acetaldehyde, *i.e.*, it had a repeat unit of C_2H_4O. There are three possible structures for this polymer :

(1) $-\underset{CH_3}{CH}-O-\underset{CH_2}{CH}-O-\underset{CH_3}{CH}-O-\underset{CH_2}{CH}-$ Methyl polyoxymethylene

(2) $-CH_2-\underset{OH}{CH}-CH_2-\underset{OH}{CH}-CH_2-\underset{OH}{CH}-$ Polyvinyl alcohol

(3) $-O-CH_2-CH_2-O-CH_2-CH_2-$ Polyethylene oxide

Polyvinyl alcohols are well known : they are soluble in water and insoluble in most organic solvents. Polyethylene oxides are also soluble in water. The polymer from acetaldehyde is insoluble in water though soluble in acetone and benzene. Methyl-substituted polyoxymethylenes corresponding to structure (1) do not appear to have been described. Of the three alternatives this structure requires the least reorganisation of the acetaldehyde molecule and on chemical evidence appears to be the most plausible.

One of the possible configurations of an alternating carbon–oxygen chain gives repeat distances of 3·86 A. and 7·70 A.

Discussion.—The experiments described above suggest that the uncatalysed low-temperature polymerisation of acetaldehyde is an entirely new type of reaction. Polymerisation to form what are probably long methyl polyoxymethylene chains appears to take place when the acetaldehyde is in the act of crystallising from the liquid. The slower this process the greater the extent of the polymerisation. The high viscosity and low number average molecular weight of the polymerised aldehyde suggest that a relatively small number of long chains are formed.

It would appear that as the acetaldehyde freezes chemical interaction can on rare occasion occur between successive molecules which attach themselves to the crystal lattice. (The necessary activation energy may probably be derived from the latent heat of fusion.) A free valency is thereby formed, and succeeding molecules as they orient themselves to join the lattice apparently form fresh chemical bonds with some ease and so build up the long chain. It is clear that the interposition of a molecule of another substance in place of acetaldehyde would break this chain. This would explain the sensitivity of the reaction to the presence of impurities, the polymerisation being strongly inhibited by the presence of small amounts of other substances, even of polymer formed in an earlier partial polymerisation.

The reason for the ease of depolymerisation is not clear, but it is probably significant that methyl polyoxymethylenes do not appear to have been previously described, this fact indicating their relative instability.

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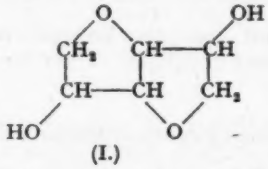
60. *Anhydrides of Polyhydric Alcohols. Part IX. Derivatives of 1 : 4-Anhydrosorbitol from 1 : 4-3 : 6-Dianhydrosorbitol.*

By R. MONTGOMERY and L. F. WIGGINS.

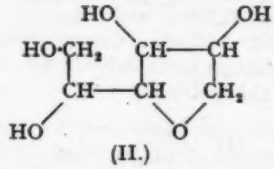
Ring scission of 1 : 4-3 : 6-dianhydrosorbitol with hydrochloric acid gives rise to 1 : 6-dichloro sorbitol and 6-chloro 1 : 4-anhydrosorbitol. Exceptional properties of 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol are described.

WHEN sorbitol is heated with acid catalysts it readily undergoes dehydration to form anhydrocompounds. Thus, Montgomery and Wiggins (this vol., p. 433) found that high yields of a dianhydrosorbitol were obtained when sorbitol was heated with sulphuric, hydrochloric, or *p*-toluenesulphonic acids until dehydration was complete. Soltzberg, Goepp, and Freudenberg (*J. Amer. Chem. Soc.*, 1946, **68**, 919) found however that, if the reaction was allowed to proceed for only a short time, a monoanhydrosorbitol was formed. The dianhydrosorbitol has been shown to possess the 1 : 4-3 : 6 ring structure by Montgomery and Wiggins (*J.*, 1946, 390) and by Hockett, Fletcher, Sheffield, and Goepp (*J. Amer. Chem. Soc.*, 1946, **68**, 927). The constitution of the monoanhydrosorbitol has been shown [Soltzberg, Goepp, and Freudenberg

(*loc. cit.*); Hockett, Conley, Yusem, and Mason, *J. Amer. Chem. Soc.*, 1946, **68**, 922] to be that of 1 : 4-anhydrosorbitol (II). Thus, the dehydration of sorbitol proceeds in such a way that anhydridisation between C_1 and C_4 occurs with greater ease than that between C_3 and C_6.



(I.)

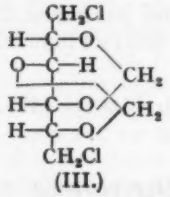


(II.)

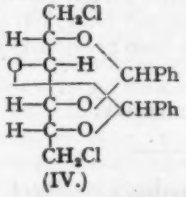
Experiments have now been carried out on the ring scission of 1 : 4-3 : 6-dianhydrosorbitol and evidence obtained that the pentaphane ring in the 3 : 6-position is more easily broken than the 1 : 4-anhydro-ring. When dianhydrosorbitol was heated for a short time under pressure with fuming hydrochloric acid, it was partly converted into a dichloro sorbitol (*a*) [isolated as a dibenzylidene derivative (*A*)] and a monochloro anhydrosorbitol (*b*) [isolated as a monobenzylidene derivative (*B*)].

When (*A*) was treated with paraformaldehyde and sulphuric acid, the benzylidene residues were replaced by methylene groups giving 1 : 6-dichloro 2 : 4-3 : 5-dimethylene sorbitol (III) the constitution of which had already been determined (Haworth and Wiggins, *J.*, 1944, 58). Therefore in (*A*) the chlorine atoms must be attached to C_1 and C_6, and (*A*) must have arisen through scission of both the 1 : 4- and the 3 : 6-ring of dianhydrosorbitol, the chlorine atoms having attached themselves to both primary carbon atoms. The orientation of the benzylidene residues in (*A*) is, however, on this evidence alone not certain. Nevertheless, by analogy with such compounds as 1 : 6-dibenzoyl 2 : 4-3 : 5-dimethylene mannitol, 1 : 6-dibenzoyl 2 : 4-3 : 5-dimethylene sorbitol, and 1 : 3-2 : 4-dibenzylidene, 1 : 3-2 : 4-dimethylene, and 1 : 3-2 : 4-diethylidene sorbitol, in all of which the aldehyde residues are linked in acetal formation to alternate carbon atoms, the most likely allocation of the benzylidene groups in this compound will be to $C_2 : C_4$ and $C_3 : C_5$, and thus (*A*) must be 1 : 6-*dichloro* 2 : 4-3 : 5-*dibenzylidene sorbitol* (IV).

It is reasonable to suppose that substance (*b*) arises through the scission of either the 1 : 4- or the 3 : 6-anhydro-ring of dianhydrosorbitol with the addition of the chloride ion to the primary carbon atom so released. It is certainly well known in the sugar series that when ethylene oxide anhydro-rings involving primary carbon atoms suffer ring scission, the entering anion attaches itself mainly to that atom, in which case there can be no question of Walden inversion occurring. Thus there are two possible structures for (*b*), namely 6-chloro 1 : 4-anhydrosorbitol (V) and 1-chloro 3 : 6-anhydrosorbitol (VI).



(III.)



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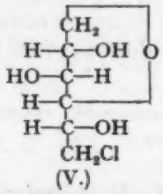
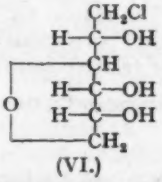
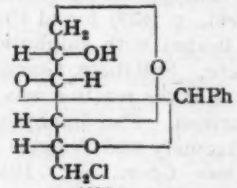


(V.)

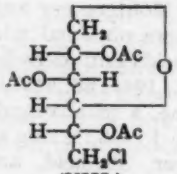


(VI.)

We know, however, that 1 : 4-anhydrosorbitol can be obtained in fair yield from sorbitol (Soltzberg, Goepp, and Freudenberg, *loc. cit.*), and therefore the 1 : 4-ring is probably more stable than the 3 : 6-ring, so that as a working hypothesis the structure (V) is considered most likely for (*b*). The benzylidene derivative (*B*) can then only have the structure (VII), that is, with the benzylidene residue allotted to C_3 and C_5. The other possible allocations of the benzylidene group, *i.e.*, between C_2 and C_3 or between C_2 and C_5, are precluded on stereochemical grounds by a study of the scale-models. The chemical properties of (*B*) prove the correctness of this supposition.



(VII.)



(VIII.)

Treatment of (*B*) with sodium iodide in acetone solution effected the liberation of 80% of the theoretical yield of sodium chloride. This exchange of a chlorine for an iodine atom in (*B*) provides evidence for the supposition that the chlorine atom is attached to a primary carbon atom which, though not quite unequivocal, is very strong, since it is known that the chlorine atoms in 1 : 6-dichloro 2 : 4-3 : 5-dimethylene mannitol can be almost quantitatively exchanged for iodine atoms with the formation of 1 : 6-di-iodo 2 : 4-3 : 5-dimethylene mannitol (Micheel, *Annalen*, **1942**, **496**, 77), whereas the chlorine atoms in 2 : 5-dichloro 1 : 4-3 : 6-dianhydromannitol do not react with sodium iodide in acetone (Wiggins, *J.*, 1945, 4).

(*B*) is stable in the cold towards sodium methoxide, a reagent which promotes anhydro-ring formation when this is readily possible, so the free hydroxyl group in (*B*) cannot be in such a position as to engage in ring formation. Structure (VII) agrees with this fact.

On removal of the benzylidene residue from (*B*) by hydrolysis with oxalic acid, there is obtained a crystalline chloro anhydrosorbitol which, if formula (VII) is correct, will be 6-*chloro* 1 : 4-*anhydrosorbitol* (V). This on acetylation yields 6-*chloro* 2 : 3 : 5-*triacetyl* 1 : 4-*anhydrosorbitol* (VIII). Further evidence of the correctness of structure (VII) for (*B*) is adduced from the fact that treatment of (VIII) with sodium methoxide yields 1 : 4-3 : 6-dianhydrosorbitol, isolated as its 2 : 5-bismethanesulphonyl derivative, though this reaction is complicated in as much as another methanesulphonyl derivative of unknown constitution is also formed. That 1 : 4-3 : 6-dianhydrosorbitol is formed, however, proves the presence of one hydrofuranol ring in (*B*); that the ring is in the 1 : 4-position is proved by the fact that treatment of (*B*) with thionyl chloride and pyridine gave the same product as was prepared from 1 : 4-anhydrosorbitol itself, namely, bis-(6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol) 2 : 2′-sulphite (see following paper). Therefore, proof that (*B*) is 6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* is complete.

The benzylidene group in (*B*) has, however, somewhat curious properties which require comment.

It was found that the benzylidene residue was partly removed by boiling the compound with distilled water, and that if steam distillation conditions were employed the hydrolysis, adjudged by the yield of benzaldehyde *p*-nitrophenylhydrazone obtained from the distillate, was complete. The original compound (*B*) could be recovered in fair yield from the non-volatile residues after rebenzylidenation, but the residues on acetylation yielded two products, 6-chloro 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol and 2 : 5-*diacetyl* 1 : 4-3 : 6-*dianhydrosorbitol* identical with a specimen prepared from dianhydrosorbitol. Therefore, although the main reaction has been merely the removal of the benzylidene group, some cyclisation between C_6 and C_3 has also occurred.

It might be considered possible that dissolved carbon dioxide was making the distilled water (pH 5·5) sufficiently acid to initiate the hydrolysis of the benzylidene residues. This was, however, not the case, since (*B*) on treatment with potassium hydroxide solution under steam distillation conditions lost benzaldehyde in the same way, although the yield of benzaldehyde isolated as the *p*-nitrophenylhydrazone was only 48% of the theoretical; this was, however, probably due to some of the benzaldehyde undergoing the Cannizzaro reaction.

This then must be a case in which a benzylidene acetal of a polyhydroxy-compound is unstable to alkali, a phenomenon so rare in the sugar or sugar alcohol series that the authors are unaware of another example.

Experimental.

Action of Fuming Hydrochloric Acid on 1 : 4-3 : 6-*Dianhydrosorbitol.*—Dianhydrosorbitol (40 g.) was heated in a sealed tube with fuming hydrochloric acid (200 c.c.) for 1 hour at 110°. The liquid was then evaporated under reduced pressure and the residual hydrochloric acid removed as far as possible by continuous distillation with water. Complete removal of the water gave a syrup which was benzylidenated by shaking with freshly distilled benzaldehyde (200 c.c.) and anhydrous zinc chloride (40 g.) for 24 hours. The product was neutralised by adding sodium carbonate (80 g.) dissolved in water, the excess of benzaldehyde removed by steam distillation under reduced pressure, and the solution evaporated to dryness. The last traces of water were removed by distillation with benzene, and the dry residue extracted 6 times with 100 c.c. portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to dryness. From this residue, by fractional recrystallisation from chloroform–petrol, were isolated 1 : 6-*dichloro dibenzylidene sorbitol* (1 g.), m. p. 223—224°, $[\alpha]_D^{18°}$ — 16·4 (*c*, 0·730 in chloroform) (Found: C, 60·7; H, 5·3; Cl, 18·4. $C_{20}H_{20}O_4Cl_2$ requires C, 60·7; H, 5·1; Cl, 18·0%), 6-*chloro* 3 : 5-*benzylidene* 1 : 4-*anhydrosorbitol* (10·4 g.), m. p. 154—155°, $[\alpha]_D^{19°}$ — 17·4 (*c*, 0·810 in chloroform) (Found: C, 57·6; H, 5·4; Cl, 12·4. $C_{13}H_{15}O_4Cl$ requires C, 57·8; H, 5·5; Cl, 13·1%), and unchanged 1 : 4-3 : 6-dianhydrosorbitol (17 g., m. p. 61—63°).

In an experiment in which the heating at 110° was continued for 2 hours instead of 1 hour, 1 : 6-dichloro dibenzylidene sorbitol (2·6 g.), 6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (25·5 g.), and 1 : 4-3 : 6-dianhydrosorbitol (4·0 g.) were isolated in the same way as described above. 6-Chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol, on treatment with sodium iodide in acetone at 100° for 5 hours under anhydrous conditions, gave 80% of the theoretical yield of sodium chloride.

1 : 6-*Dichloro* 2 : 4-3 : 5-*Dimethylene Sorbitol.*—1 : 6-Dichloro dibenzylidene sorbitol (1 g.) was warmed with paraformaldehyde (1 g.) and concentrated sulphuric acid (4 drops) for about 20 minutes. The product was then shaken with chloroform overnight and the extract washed with concentrated ammonia solution and with water, dried, and the solvent evaporated. The syrupy product was dissolved in alcohol from which crystallised 1 : 6-dichloro 2 : 4-3 : 5-dimethylene sorbitol (0·3 g.), m. p. 116—117°, alone or in admixture with an authentic specimen.

Treatment of 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol with Sodium Methoxide.*—To the compound (2·68 g.) dissolved in chloroform and cooled to 0° was added an ice-cold solution of sodium (0·25 g.) in dry methyl alcohol (10 c.c.). The mixture was kept overnight at room temperature and thereafter diluted with chloroform. The chloroform layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of the chloroform solution and recrystallisation of the residue from chloroform–petrol gave the original compound (2·6 g.), m. p. 154—155°.

Hydrolysis of 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—The compound (10 g.) was heated under reflux for 6 hours with oxalic acid (15 g.) dissolved in acetone (400 c.c.) and water (50 c.c.). The solution was then neutralised with barium carbonate, filtered, and the acetone removed from the filtrate under reduced pressure. On cooling the residual solution, some of the original compound (3·6 g.) separated and was filtered off. The filtrate was filtered and evaporated to dryness under reduced pressure, and the residue recrystallised from ethyl acetate. It was 6-*chloro* 1 : 4-*anhydrosorbitol*, m. p. 108—109°, $[\alpha]_D^{14°}$ − 14·0° (*c*, 2·9 in acetone). Yield, 1·9 g. (Found: C, 39·7; H, 6·1; Cl, 20·0. $C_6H_{11}O_4Cl$ requires C, 39·6; H, 6·0; Cl, 19·5%). The residues from the crystallisation were acetylated to give 6-chloro 2 : 3 : 5-triacetyl 1 : 4-anhydrosorbitol (2·2 g.), m. p. 81—82° (see below).

Action of Sodium Methoxide on 6-*Chloro* 1 : 4-*Anhydrosorbitol.*—6-Chloro 1 : 4-anhydrosorbitol (0·85 g.) was dissolved in dry methyl alcohol (5 c.c.) and added to dry methyl alcohol (4 c.c.) containing sodium (0·117 g.). After 24 hours at room temperature the solution was exactly neutralised with dilute sulphuric acid and evaporated to dryness under reduced pressure. The residue was extracted with ethyl acetate, the extract dried ($MgSO_4$) and evaporated. The syrupy product (0·5 g.) was dissolved in dry pyridine (15 c.c.), and methanesulphonyl chloride (1·3 c.c.) carefully added at 0°. The mixture was kept at room temperature for 24 hours and then poured into water. The aqueous solution was extracted several times with chloroform, and the combined extracts were washed successively with 5N-sulphuric acid, sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). The chloroform was then removed, and the residue, which only partly crystallised, was fractionally recrystallised, giving 2 : 5-bismethanesulphonyl 1 : 4-3 : 6-dianhydrosorbitol, m. p. 121—122°, alone or in admixture with an authentic specimen (see following paper), and a substance, m. p. 82—83°, of unknown constitution. A fraction of m. p. 114° was apparently impure 2 : 5-bismethanesulphonyl dianhydrosorbitol.

Action of Water on 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—(*a*) A suspension of the compound (0·558 g.) in distilled water (50 c.c.) was distilled at constant volume until no more benzaldehyde was produced. The benzaldehyde in the distillate, estimated as the *p*-nitrophenylhydrazone, was 0·208 g. (95%).

The residue in the distillation flask was evaporated under reduced pressure, and the syrupy product (0·3 g.) was shaken with benzaldehyde (10 c.c.) and anhydrous zinc chloride for 12 hours. The benzylidene derivative, isolated in the usual way and recrystallised from chloroform–petrol, had m. p. 154—155°, alone or in admixture with the original compound.

(*b*) A suspension of the compound (5 g.) in distilled water (150 c.c.) was distilled at constant volume until no more benzaldehyde was produced. The solution was then evaporated to dryness under reduced pressure, and the syrupy product (2·7 g.) acetylated with acetic anhydride (10 c.c.) and fused sodium acetate (2 g.). The product was a syrup, which distilled b. p. 190—200° (bath temp.)/10 mm. The distillate partly crystallised, and after recrystallisation from alcohol showed m. p. 81—82°, $[\alpha]_D^{18°}$ − 21·9° (*c*, 1·550 in chloroform). It was 6-*chloro* 2 : 3 : 5-*triacetyl* 1 : 4-*anhydrosorbitol*. Yield, 0·9 g. (Found: C, 47·1; H, 5·6. $C_{12}H_{17}O_7Cl$ requires C, 46·8; H, 5·5%). The mother liquor from the recrystallisation was evaporated; the residue crystallised, and after recrystallisation from alcohol had m. p. 60—61° alone or in admixture with authentic 2 : 5-diacetyl 1 : 4-3 : 6-dianhydrosorbitol (see below). Yield, 2·3 g.

2 : 5-*Diacetyl* 1 : 4-3 : 6-*Dianhydrosorbitol.*—1 : 4-3 : 6-Dianhydrosorbitol (10 g.) was mixed with fused sodium acetate (10 g.) and acetic anhydride (30 c.c.) and the mixture heated under reflux for 1½ hours. The solution was cooled and poured on to ice. The precipitated syrup slowly crystallised. The *diacetate* was filtered off, washed with water and recrystallised from alcohol, m. p. 60—61° $[\alpha]_D^{18°}$ − 133·6° (*c*, 2·29 in chloroform) (Found: C, 52·4; H, 5·9. $C_{10}H_{14}O_6$ requires C, 52·2; H, 6·1%).

Action of Aqueous Potassium Hydroxide on 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—(*a*) The compound (4·5 g.) was heated under reflux for 2 hours with potassium hydroxide (2·1 g., 2 mols.) in water (60 c.c.). The compound quickly dissolved, and the solution developed a slight brown colouration with an odour of benzaldehyde which increased as the reaction proceeded. The resulting solution was cooled, and the solid, which crystallised as long needles, m. p. 154—155°, was identified as the original compound. The aqueous mother liquor was exactly neutralised with dilute hydrochloric acid and evaporated to dryness. Recrystallisation of the residue from chloroform–petrol gave the unchanged compound together with an uncrystallisable syrup.

(*b*) A suspension of the compound (1·846 g.) in distilled water was submitted to steam distillation in the presence of potassium hydroxide (0·88 g., 2 mols.) until no more benzaldehyde distilled. The benzaldehyde in the aqueous distillate, estimated as the *p*-nitrophenylhydrazone, was 0·346 g.(48%).

Action of Thionyl Chloride on 6-*Chloro* 3 : 5-*Benzylidene* 1 : 4-*Anhydrosorbitol.*—6-Chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol (0·5 g.) was dissolved in dry pyridine (0·5 c.c.) and the solution cooled to 0°. After addition of a little anhydrous magnesium sulphate, thionyl chloride (0·2 c.c.) was added and the mixture kept for 2 hours at room temperature, and then 2 hours on a boiling water-bath. The mixture was cooled, poured on ice-water, and the chloro-compound extracted with chloroform. The combined chloroform extracts were washed successively with 5N-sulphuric acid, 10% sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). The chloroform solution was then

evaporated and the residue recrystallised from alcohol. Yield, 0·2 g., $[\alpha]_D$ − 47·0° (*c*, 1·49 in chloroform), m. p. 107°, alone or in admixture with authentic specimen (see following paper) of bis-(6-chloro 3 : 5-benzylidene 1 : 4-anhydrosorbitol) 2 : 2′-sulphite.

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NOTES.

Some Derivatives of p-*Aminobenzoic Acid.* By A. T. FULLER, C. R. HARINGTON, ROSALIND PITT RIVERS, and JOAN M. L. STEPHEN.

AMONG derivatives of *p*-aminobenzoic acid which have been studied for their effect on bacterial growth, those in which the amino-group itself carries a basic substituent have hitherto escaped attention. Of the compounds whose synthesis is described below only one, namely 4-amino-4′-carboxydiphenylamine, shows significant antibacterial activity; this inhibits *Strep. hæmolyticus*, *Staph. aureus*, and *B. coli* in broth and synthetic media to about the same extent as sulphanilamide; in blood it is rapidly oxidised and is considerably less active. Testing of several of the compounds was limited by their insolubility. They showed no activity against acid-fast organisms, and none of them had more than a trace of anti-sulphonamide action.

N-*Acridyl*(5)-p-*aminobenzoic Acid.*—5-Chloroacridine (2·1 g.) was heated with phenol (10 g.) on the boiling water-bath for 15 minutes; anhydrous potassium carbonate (1·4 g.) and *p*-aminobenzoic acid (1·37 g.) were added and heating was continued for 14 hours. After cooling, the phenol was removed with ether and the residue taken up in hot 50% alcohol with addition of ammonia; on neutralisation with acetic acid the *acid* separated in glistening orange plates. Yield, 90%. M. p. 289—290° (decomp.) (Found: N, 9·0. $C_{20}H_{14}O_2N_2$ requires N, 8·9%).

N-8-*Chloro*-3-*methoxyacridyl*(5)-p-*aminobenzoic Acid.*—This *acid* was prepared as above, starting from 5 : 8-dichloro-3-methoxyacridine. Yield, 87% of scarlet prisms, m. p. 310—312° (decomp.) (Found: N, 7·2. $C_{21}H_{15}O_3N_2Cl$ requires N, 7·4%).

N-*Pyridyl*(4)-p-*aminobenzoic Acid.*—4-Chloropyridine (8 g.) and *p*-aminobenzoic acid (9·5 g.) in glacial acetic acid (28 c.c.) were boiled under reflux for 4 hours. The crystalline *hydrochloride* which separated on cooling was collected. It formed colourless needles, m. p. 264°. Yield, 60% (Found: N, 10·5. $C_{12}H_{10}O_2N_2,HCl,H_2O$ requires N, 10·4%).

The free *pyridylaminobenzoic acid* crystallised in clusters of colourless needles when the aqueous solution of the hydrochloride was treated with 1 equiv. of sodium hydroxide. M. p. 318—320° (decomp.) (Found: N, 13·0. $C_{12}H_{10}O_2N_2$ requires N, 13·1%).

N-*Quinolyl*(4)-p-*aminobenzoic Acid.*—4-Chloroquinoline (9·0 g.) and *p*-aminobenzoic acid (7·5 g.) in acetic acid (25 c.c.) were boiled under reflux; after 2 minutes the contents of the flask solidified. Heating was continued for 1 hour on the water-bath, after which the mixture was cooled, ground with 50% aqueous acetic acid, and the solid collected. The product was dissolved in 50% alcohol with the aid of sodium hydroxide and neutralised at the boiling point with acetic acid. The *acid* crystallised in pale yellow needles, m. p. 314—316° (decomp.). Yield, 75% (Found: N, 10·5. $C_{16}H_{12}O_2N_2$ requires N, 10·6%).

N-*Quinolyl*(2)-p-*aminobenzoic Acid.*—This *acid* was obtained similarly (heating for 3 hours) from 2-chloroquinoline. Yield, 56% of pale yellow needles after recrystallisation from 50% dioxan. M. p. 285—286° (Found: N, 10·7%).

4-*Nitro*-4′-*carboxydiphenylamine.*—Dry sodium *p*-bromobenzoate (11·1 g.) was ground with anhydrous potassium carbonate (6·9 g.) and the mixture was added to a solution of *p*-nitroaniline (6·9 g.) in nitrobenzene (25 c.c.) containing activated copper (0·2 g.) and potassium iodide (0·2 g.) and heated to 130°. The temperature was raised to 190—210° at which level it was held for 24 hours. The nitrobenzene and unchanged nitroaniline (66% recovery) were removed by steam distillation and the solution filtered from tar and somewhat concentrated. On chilling, a sodium salt separated in red needles (yield, 46% allowing for the recovered nitroaniline) from which was obtained the free *acid*; this formed stumpy orange-brown needles from aqueous alcohol, m. p. 278° (Found: N, 11·2. $C_{13}H_{10}O_4N_2$ requires N, 10·9%).

4-*Amino*-4′-*carboxydiphenylamine.*—The sodium salt of the above nitro-acid (1·4 g.) was dissolved in aqueous ammonia and treated with hydrated ferrous sulphate (8·75 g.). After 10 minutes on the boiling water-bath the mixture was filtered; the precipitate of ferric hydroxide was extracted with boiling water and the combined filtrate and extract were acidified with acetic acid at the boiling point. After rapid filtration the solution was chilled in ice; the *acid* then separated in colourless prisms which darkened rapidly on exposure to air. It could be recrystallised from water or from xylene–ligroin. Yield, 77%. M. p. 205° (decomp.) (Found: N, 12·5. $C_{13}H_{12}O_2N_2$ requires N, 12·3%).—NATIONAL INSTITUTE FOR MEDICAL RESEARCH, HAMPSTEAD, N.W.3. [*Received, March 13th*, 1947.]

Rapid Preparation of a Solution of Sodium Hydrogen Sulphide.

By Herbert H. Hodgson and Edward R. Ward.

Previous work on this subject includes that of Stromeyer (*Annalen*, 1858, **107**, 333) who reported that carbon dioxide decomposed a solution of sodium sulphide, and that the latter evolved hydrogen sulphide when treated with sodium hydrogen carbonate, sodium carbonate being formed. No specific details are, however, available for the preparation of sodium hydrogen sulphide by reaction between equivalent amounts of sodium sulphide and sodium hydrogen carbonate, with subsequent use of alcohol to obtain the pure solution of hydrosulphide (cf. B.P. 184,795; U.S.P. 1,675,491). Earlier work by Hodgson and Birtwell on the reduction of 1 : 3-dinitronaphthalene (*J.*, 1944, 75; *J. Soc. Dyers Col.*, 1945, **61**, 171) revealed the necessity for the exclusion of sodium hydroxide and the prevention of a rise in the pH of the reduction medium for maximum reductive efficiency of sodium sulphide. Their reducing agent, however, was generally prepared warm and would lead to deterioration through loss of hydrogen sulphide. Later, Hodgson and Hathway (*J.*, 1945, 123) showed that sodium hydrogen carbonate could not be efficiently replaced by sodium carbonate in Hodgson and Birtwell's experiments, and that carbon dioxide was not evolved when an aqueous solution containing equivalent amounts of sodium hydrogen carbonate and sodium sulphide was heated. Finally, Hodgson and Ward (*J.*, 1945, 590, 663, 794) found that the reductive efficiency of the above mixture was superior to that of sodium hydrogen sulphide prepared by treating sodium hydroxide with hydrogen sulphide, or by the addition of hydrochloric acid to a solution of sodium sulphide (cf. Lapworth and Pearson, *J.*, 1921, **119**, 765; Lapworth and Haworth, *ibid.*, p. 768), in which much hydrogen sulphide is lost even by working in a tall cylinder at 0°.

A method is now described, whereby a comparatively concentrated solution of almost pure sodium hydrogen sulphide (96—98% of the calculated amount of NaSH) in aqueous methanol or ethanol can be rapidly prepared which contains only a negligible amount of sodium carbonate. Almost all the sodium carbonate formed by the reaction of the sodium sulphide and sodium hydrogen carbonate in aqueous methanol is precipitated as the crystalline monohydrate with a small amount of " occluded " sulphide. Other reagents such as boric acid, sodium hydrogen phosphate, oxalic acid, tartaric acid, and sodium hydrogen sulphate are unsuitable. Ethanol is nearly as efficient as methanol but acetone is unsuitable.

When an *aqueous* solution of sodium sulphide is treated with solid sodium hydrogen carbonate, precipitation of sodium carbonate decahydrate slowly takes place, but this is far from complete even after long standing at 15°.

Similar methods cannot be used to prepare pure aqueous alcoholic potassium hydrogen sulphide, owing to the much greater solubility of potassium carbonate in methanol or ethanol, and the alternative reactants above also proved unsuitable.

Experimental.—A concentrated aqueous solution of sodium sulphide is prepared by dissolution of the pure (" AnalaR ") nonahydrate ($\lessapprox$ 95% $Na_2S,9H_2O$) in freshly distilled water, and then diluted to contain 13% Na_2S w/v. Finely powdered sodium hydrogen carbonate (14 g.; 99·8% purity) is then stirred into the above solution (100 c.c.) below 20°; it dissolves at once with evolution of heat. Methyl alcohol (100 c.c.) is next added with stirring, also below 20°; there is further evolution of heat, and almost complete precipitation of crystalline sodium carbonate occurs immediately. After 30 minutes, the mixture is filtered at the pump, and the residue washed portionwise with methyl alcohol (50 c.c.). The filtrate now contains sodium hydrogen sulphide ($\lessapprox$ 9 g.) and a little sodium carbonate ($\gtrsim$ 0·6 g.), the respective concentrations being *ca.* 3·5 g. and 0·2 g. per 100 c.c. of solution.

(*a*) For ordinary purposes, it is sufficient to dissolve equivalent amounts of sodium sulphide nonahydrate and sodium hydrogen carbonate in the required amount of water, add the necessary volume of methyl alcohol and filter off the precipitated sodium carbonate; the filtrate can then be used forthwith for reduction.

(*b*) When more concentrated solutions of sodium sulphide are employed, the precipitated sodium carbonate contains " occluded " sulphide.

(*c*) The solution of sodium hydrogen sulphide, which is only faintly alkaline to phenolphthalein, can be kept in a stoppered bottle for at least a week with but slight deterioration.

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Structural Relationships in the Natural Unsaturated Higher Fatty Acids.

A Lecture delivered before the Chemical Society on January 8th, 1948.

By T. P. Hilditch, D.Sc., F.R.I.C., F.R.S.

In natural fats and fatty oils the most familiar, and indeed also the most abundant, constituent acid is oleic (*cis-n*-octadec-9-enoic), $CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$, but nearly forty analogous natural unsaturated acids have so far been recorded in various fats, and of these the constitutional formulæ are, for the most part, known with reasonable certainty. A large number of these naturally occurring unsaturated fatty acids contain the same normal carbon chain of eighteen carbon atoms which is present in oleic acid, but in others the chain may be shorter or longer. Unsaturated acids containing as few as ten, and as many as twenty-six, carbon atoms in their molecules have been reported, and all the intervening "even-numbered" members are represented in the natural acids. Those belonging to the C_{16}, C_{20}, and C_{22} series are, however, more abundant than any others except those with a chain of eighteen carbon atoms. Moreover, in different kinds of natural fats, all degrees of unsaturation from monoethenoid to hexaethenoid occur in their unsaturated acids; but polyethenoid unsaturation is much more frequent in the longer chain (C_{18} and upwards) than in the shorter chain acids. Indeed, no natural polyethenoid fatty acid containing less than sixteen carbon atoms has yet been observed.

Many of these acids share common constitutive features, and attention will be largely directed, in the present discussion, to considering these similarities in structure and their possible implications in regard to the genesis of the natural fatty acids in the living organism. Before doing so, however, it is perhaps desirable to try to obtain in rough perspective the relative quantities of the many different fatty acids which are so freely produced in different organisms. From a quantitative standpoint, the amount of many of the unsaturated acids produced in nature is extremely small (and often restricted to a single species or group of related species) in comparison with the relatively abundant production of a few—notably oleic, linoleic, hexadecenoic (palmitoleic), and the highly unsaturated acids of the C_{20} and C_{22} series which are especially typical of fats from marine organisms.

It is of course not possible to offer even a rudimentary statistical estimate of the natural production in the world of individual fatty acids, since data as to the total production in Nature of different fats are largely lacking, even in those cases (still only a fraction) in which the proportions of their component acids are known. Some years ago, however, the Dutch chemist Boekenoogen (*Oliën Vetten Oliezadan*, **1941**, **26**, 143) made an interesting statistical survey of the fatty acids produced annually in Nature in a group of fats of industrial interest of which the world production and fatty acid compositions were both known with some approach to accuracy. His survey was limited to twenty fats from vegetable sources, including sunflower-seed, olive, groundnut, soya-bean, rape, coconut, palm-kernel, linseed, and a few other similar oils. Boekenoogen reached the conclusion that, over the range of oils employed, the percentage natural production of different fatty acids was as follows: oleic, 34; linoleic, 29; palmitic, 11; lauric, 7; linolenic, 6; myristic, stearic, and erucic (each), 3; and *all others together* 4%.

These ratios would be altered somewhat if the whole range of vegetable fats could be similarly assessed, and still more if the large amounts of fat synthesised by land animals and by marine organisms (from vegetable or animal plankton to the large fishes and marine mammals) were brought into the picture. It is not unreasonable to expect that more fat may be produced by aquatic organisms than the combined production of land vegetables and animals. At all events, fats from aquatic sources must represent a very substantial proportion of the total world production, and in these fats, although oleic again forms the major component of the fatty acids (usually of the order of $30 \pm 10\%$), important proportions of hexadec-9-enoic (palmitoleic) acid and polyethenoid unsaturated acids of the C_{20} and C_{22} series may also each amount on an average to, perhaps, $20 \pm 5\%$ of the total acids, with about 10—15% of (saturated) palmitic acid also present. Again, the main components of most land animal body fats consist of about 30% of palmitic acid with larger amounts of oleic acid and with stearic acid contents varying from about 10 to 25%; whilst their milk fats are somewhat similar in composition except for the frequent presence of about 10—20% of acids (mainly saturated) with shorter carbon chains (C_{12}, C_{10}, C_8, C_6, and C_4) than in most other fats.

Hence, although it is clearly impossible to attempt any reasonably precise estimate, one may offer the opinion that, of all the fatty acids synthesised in Nature, oleic acid probably forms not much less than about 40%, and that no other acid approaches it in amount, with the single

exception of the most characteristic member of the saturated series, palmitic, which may well form about 15% of the total natural fatty acid production. The characteristic C_{16} and C_{20-22} acids of fats of aquatic orgin, and linoleic acid which is so frequent a constituent of vegetable fats, with possibly stearic acid (mainly from certain classes of land animals), are probably the only other fatty acids which would contribute a significant individual contribution in a survey of world production; this might be (speculatively) estimated at, say, 5—7% in each case. If these figures bear any near relation to the actual facts, they imply that the rest of the natural higher fatty acids (saturated and unsaturated) together account for only about 15—25% of the total world production—and much of this proportion would be accounted for by acids such as lauric, myristic, erucic, linolenic, and a few others which predominate in seed fats of certain plant families. Thus many of the unsaturated acids to which reference will now be made are only produced in Nature in relatively minute quantities in comparison with the natural production of oleic acid and a few other unsaturated fatty acids.

Having thus endeavoured to give a picture—albeit necessarily very crude—of the relative occurrence of the many different unsaturated acids, let us now proceed to a more detailed consideration of their constitutive resemblances and dissimilarities.

Natural Unsaturated Acids which contain a Structure Identical with One or Other Half of the Oleic Acid Molecule ($CH_3{\cdot}[CH_2]_7CH{:}$ *or* $:CH{\cdot}[CH_2]_7{\cdot}CO_2H$).

Many natural straight-chain ethenoid acids of fats share a somewhat singular partial resemblance to oleic acid in that one or other part of their molecules is identical with that of one half of the oleic acid molecule.

Natural Unsaturated Acids with a Common Grouping, $:CH{\cdot}[CH_2]_7{\cdot}CO_2H$.—Table I shows the constitution of six monoethenoid acids (C_{10} to C_{20}) of the " even-numbered " homologous series in which unsaturation occurs uniformly at the 9th carbon atom from the acidic end of the molecules.

TABLE I.

Monoethenoid acids, $R{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$.

$C_{10}H_{18}O_2$	Dec-9-enoic	$CH_3{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{12}H_{22}O_2$	Dodec-9-enoic	$CH_3{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{14}H_{26}O_2$	Tetradec-9-enoic (myristoleic)	$CH_3{\cdot}[CH_2]_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{16}H_{30}O_2$	Hexadec-9-enoic (palmitoleic)	$CH_3{\cdot}[CH_2]_5{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{18}H_{34}O_2$	Octadec-9-enoic (oleic)	$CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{20}H_{38}O_2$	Eicos-9-enoic (gadoleic)	$CH_3{\cdot}[CH_2]_9{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$

On the whole, acids of exclusively animal origin preponderate in Table I, but it must be recalled that hexadecenoic acid (though only present in traces in most land vegetable fats) is as ubiquitous in Nature as is oleic acid itself, and that hexadecenoic and gadoleic acid occur in some quantity in fats of aquatic origin, vegetable as well as animal. On the other hand, the polyethenoid acids of the C_{18} series—linoleic, linolenic, elæostearic, licanic, parinaric—which are characteristic and major components of many of the more unsaturated kinds of vegetable fatty oils (illustrated in Table II) share the same constitutive feature with those of the monoethenoid acids in Table I: unsaturation begins in each at the 9th carbon atom from the carboxyl group, irrespective of whether the polyethenoid structure is conjugated or not.

TABLE II.

Polyethenoid acids, $R{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$ (*of vegetable fats*).

$C_{18}H_{32}O_2$	Octadeca-9 : 12-dienoic (linoleic)	$CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{18}H_{30}O_2$	Octadeca-9 : 12 : 15-trienoic (linolenic)	$CH_3{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{18}H_{30}O_2$	Octadeca-9 : 11 : 13-trienoic (elæostearic)	$CH_3{\cdot}[CH_2]_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$
$C_{18}H_{28}O_3$	4-Keto-octadeca-9 : 11 : 13-trienoic (licanic)	$CH_3{\cdot}[CH_2]_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}[CH_2]_4{\cdot}CO{\cdot}[CH_2]_3{\cdot}CO_2H$
$C_{18}H_{28}O_2$	Octadeca-9 : 11 : 13 : 15-tetraenoic (parinaric)	$CH_3{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}[CH_2]_7{\cdot}CO_2H$

Natural Unsaturated Acids with a Common Grouping $CH_3{\cdot}[CH_2]_7{\cdot}CH{:}$.—There are apparently just as many instances in which the converse state of affairs obtains to that considered in Tables I and II. The acids shown in Table III originate exclusively in vegetable fats, with the exception of selacholeic or nervonic (tetracos-15-enoic) acid which has been observed in the fats

of Elasmobranch fish (Tsujimoto, *J. Soc. Chem. Ind., Japan*, 1927, **30**, 1868) and of cerebrosides (Klenk, *Z. physiol. Chem.*, 1927, **66**, 287), and, of course, of oleic acid itself which is common to all fats.

TABLE III.

Monoethenoid acids, $CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_n \cdot CO_2H$.

$C_{14}H_{26}O_2$	Tetradec-5-enoic	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_3 \cdot CO_2H$
$C_{18}H_{34}O_2$	Octadec-9-enoic (oleic)	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$
$C_{20}H_{38}O_2$	Eicos-11-enoic	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_9 \cdot CO_2H$
$C_{22}H_{42}O_2$	Docos-13-enoic (erucic)	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_{11} \cdot CO_2H$
$C_{24}H_{46}O_2$	Tetracos-15-enoic (selacholeic)	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_{13} \cdot CO_2H$
$C_{26}H_{50}O_2$	Hexacos-17-enoic (ximenic)	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_{15} \cdot CO_2H$
$C_{30}H_{58}O_2$	Tricos-21-enoic (lumequic)	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_{19} \cdot CO_2H$

It is natural, owing to the universal presence of oleic acid in natural fats (usually in major proportion), to wonder whether the homologous unsaturated acids in Tables I and III may not result from some chemical transformation of pre-formed oleic acid or glycerides. At first sight this idea gains some support from the circumstance that the acid with almost the longest carbon chain in Table I, and with almost the shortest carbon chain in Table III, is oleic acid, thus suggesting (*a*) that the lower homologues in Table I might arise by shortening of the alkyl chain $CH_3 \cdot [CH_2]_7 \cdot CH{:}$ of oleic acid, and (*b*) that the higher homologues in Table III might similarly be the result of prolongation of the oleic skeleton of carbon atoms by interaction at the carboxyl group with other, shorter-chain, acidic groups. Such possibilities must be regarded for the present, however, as purely speculative.

It is, indeed, probable that the production of homologous monoethenoid acids down to dec-9-enoic acid, which is specific so far only in milk fats, is the result of shortening of the alkyl chain (two carbon atoms at a time) in the oleic groups of blood glycerides during their transformation in the mammary gland into milk-fat glycerides; further similar action may well account for the short-chain saturated acyl groups (butyric, hexoic, etc.) which characterise the milk fats (Hilditch, " Chemical Constitution of Natural Fats ", 2nd Edition, 1947, pp. 117—120, 306—310). On the other hand, the exclusive production of hexadec-9-enoic acid by degradation of oleic acid seems much less likely, since in the fats of aquatic organisms and of some bacteria and of some other lower forms of flora hexadec-9-enoic acid is a major component comparable in amount with that of oleic acid. Apart from the special case of the milk fats, it cannot yet be said that there is any real evidence to support the possible conversion *in vivo* of oleic acid or its glycerides into lower unsaturated homologues.

As regards the acids in Table III, Boekenoogen (*Fette u. Seifen*, 1939, **46**, 717), who first observed the C_{26} and C_{30} acids of this group in the seed fat of *Ximenia americana*, drew attention to the sequence of increase of four methylene groups between ethenoid and carboxylic groups in the series tetradecenoic–oleic–erucic–ximenic–lumequic acids of vegetable fats; but the implication of this is at present obscure. Moreover, the C_{24} acid conforming with the structural feature of this group is animal in origin, whilst an eicos-11-enoic acid (intermediate between oleic and erucic) has now been shown to be a minor component of seed fats (Cruciferæ) in which erucic acid occurs in quantity. At present, therefore, it seems wise merely to draw attention to the structural resemblances disclosed in Tables I and III, and to regard speculation as to the implications, if any, of the various common constitutional features as largely premature until further evidence can be provided. (Some recent investigations of seed fats of the family Cruciferæ, in which erucic acid is shown to be accompanied not only by small proportions of the eicos-11-enoic acid mentioned, but also by small amounts of a docosadienoic acid, will be referred to later in this discussion.)

Natural Unsaturated Acids which do not contain either of the C_9 *Groupings Present in Oleic Acid.*

Many natural unsaturated fatty acids are known which, unlike those listed in Tables I, II, and III, do not coincide with oleic acid in the constitution of either of the saturated carbon chains of their molecules. These acids, however, again fall into groups in which coincidences of structure are equally as well defined as in the preceding cases.

Natural Cyclic Unsaturated Acids.—A few species of the family Flacourtiaceæ, notably some of the genus *Hydnocarpus*, have long been known to produce seed fats of therapeutic value in leprosy and other skin affections, owing to their content of cyclic unsaturated acids in which the molecule terminates in a *cyclo*pentene group. Of these acids, chaulmoogric, $C_{18}H_{32}O_2$,

$C \cdot [CH_2]_{12} \cdot CO_2H$, and hydnocarpic, $C_{16}H_{28}O_2$, are the most abundant, but Cole and Cardoso

(*J. Amer. Chem. Soc.*, 1939, **61**, 2349) have shown that very small proportions of lower analogues down to $C_6H_8O_2$ accompany them; a cyclic diethenoid acid, $C_{18}H_{30}O_2$ (gorlic acid), is also often present in small quantities in these fatty oils. In chaulmoogra and the related oils, small quantities of oleic glycerides are also present, whilst some other species of this family contain no cyclic unsaturated acids, but only the more usual linoleic and oleic acids.

A summary of the natural cyclic unsaturated fatty acids is given in Table IV.

TABLE IV.

Cyclic unsaturated acids.

$C_{18}H_{32}O_2$	Chaulmoogric	13-*cyclo*Pent-2-enyl-*n*-tridecoic
$C_{18}H_{30}O_2$	Gorlic	13-*cyclo*Pent-2-enyl-*n*-tridec-6-enoic
$C_{16}H_{28}O_2$	Hydnocarpic	11-*cyclo*Pent-2-enyl-*n*-undecoic
$C_{14}H_{24}O_2$	Alepric	9-*cyclo*Pent-2-enyl-*n*-nonoic
$C_{12}H_{20}O_2$	Aleprylic	7-*cyclo*Pent-2-enyl-*n*-heptoic
$C_{10}H_{16}O_2$	Aleprestic	5-*cyclo*Pent-2-enyl-*n*-pentoic
$C_6H_8O_2$	Aleprolic	*cyclo*Pent-2-enylcarboxylic

Natural Unsaturated Acids with a Common Grouping, $\cdot CH{\cdot}[CH_2]_4{\cdot}CO_2H$.—An isomer of oleic acid, *cis*-octadec-6-enoic (petroselinic) acid, was discovered by Vongerichten and Köhler (*Ber.*, 1909, **42**, 1638) in parsley-seed oil, and has since been found to be present in all other seed fats of the Umbelliferæ which have been examined, and also in the seed fat of ivy and of a few rare species of tropical plants belonging to the Simarubaceæ. No diethenoid acid similarly corresponding to linoleic acid has yet been reported, but Heiduschka and Luft (*Arch. Pharm.*, 1919, **257**, 33) observed that the fatty oil from evening-primrose seeds contains an octa-6 : 9 : 12-trienoic acid isomeric with linolenic acid; whilst as already mentioned the cyclic gorlic acid contains an ethenoid bond in the aliphatic chain in the Δ^6-position.

Perhaps the most arresting feature in this group, however, is the occurrence of a natural ethynoid acid, tariric acid, in the seed fats of a few species of *Picramnia*, a South American genus of the Simarubaceæ family. This almost unique appearance of an acetylenic fatty acid has been rivalled recently by the discovery of a still more unusual acid in the glycerides of the seed fat of *Onguekoa Gore*, a West African shrub, a fatty oil which is also abnormal in its content of hydroxy-unsaturated glycerides. Steger and van Loon (*Fette u. Seifen*, 1937, **44**, 243) first reported the presence in the fat of a diethynoid acid which they termed isanic acid, but Boekenoogen (*ibid.*, p. 344) and Castille (*Annalen*, 1939, **543**, 104) showed that the acid (termed by them erythrogenic acid) was even more remarkable in that it contained a terminal vinyl group and two acetylenic groups; it differs from tariric acid in that the first acetylenic group is in the Δ^9 and not the Δ^6 position; and its possible structures are shown in Table V, which also incorporates the other natural unsaturated acids which belong structurally to this group. It will be noticed that all the acids in Table V belong to the C_{18} series.

TABLE V.

Ethenoid and ethynoid acids, $R{\cdot}C(H){:}C(H){\cdot}[CH_2]_4{\cdot}CO_2H$.

$C_{18}H_{34}O_2$	Octadec-6-enoic (petroselinic)	$CH_3{\cdot}[CH_2]_{10}{\cdot}CH{:}CH{\cdot}[CH_2]_4{\cdot}CO_2H$
$C_{18}H_{30}O_2$	Octadeca-6 : 9 : 13-trienoic	$CH_3{\cdot}[CH_2]_4{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}[CH_2]_4{\cdot}CO_2H$
$C_{18}H_{32}O_2$	Octadec-6-ynoic (tariric)	$CH_3{\cdot}[CH_2]_{10}{\cdot}C{\equiv}C{\cdot}[CH_2]_4{\cdot}CO_2H$
$C_{18}H_{26}O_2$	Octadec-17-endi-9 : (11 or 15)-ynoic	$CH_2{:}CH{\cdot}[CH_2]_4{\cdot}C{\equiv}C{\cdot}C{\equiv}C{\cdot}[CH_2]_7{\cdot}CO_2H$ or $CH_2{:}CH{\cdot}C{\equiv}C{\cdot}[CH_2]_4{\cdot}C{\equiv}C{\cdot}[CH_2]_7{\cdot}CO_2H$

Natural Unsaturated Acids with a Common Grouping, $\cdot CH{\cdot}[CH_2]_9{\cdot}CO_2H$.—There remain a few monoethenoid acids in which 9 methylene groups separate the carboxyl group from the double bond. These are illustrated in Table VI.

TABLE VI.

Monoethenoid acids, $CH_3{\cdot}[CH_2]_n{\cdot}CH{:}CH{\cdot}[CH_2]_9{\cdot}CO_2H$.

$C_{18}H_{34}O_2$	Octadec-11-enoic (vaccenic)	$CH_3{\cdot}[CH_2]_5{\cdot}CH{:}CH{\cdot}[CH_2]_9{\cdot}CO_2H$
$C_{20}H_{38}O_2$	Eicos-11-enoic	$CH_3{\cdot}[CH_2]_7{\cdot}CH{:}CH{\cdot}[CH_2]_9{\cdot}CO_2H$
$C_{22}H_{42}O_2$	Docos-11-enoic (cetoleic)	$CH_3{\cdot}[CH_2]_9{\cdot}CH{:}CH{\cdot}[CH_2]_9{\cdot}CO_2H$

Vaccenic acid was first observed by Bertram (*Biochem. Z.*, 1928, **197**, 433) in beef fat and butter fat, in both of which it is present only in minute proportions; Bertram considered it to be *trans*-octadec-11-enoic acid in view of the scission products obtained from it on oxidation.

Since his work appeared, the structure of the acid does not appear to have received independent confirmation. Boeseken, van Krimpen, and Blanken (*Rec. Trav. chim.*, 1930, **49**, 247), however, showed that *trans*-octadec-11-enoic acid, identical with the natural vaccenic acid, was present amongst the products of partial hydrogenation of elæostearic esters.

Eicos-11-enoic acid was first observed by McKinney and Jamieson (*Oil and Soap*, 1936, **13**, 289) and by Green, Hilditch, and Stainsby (*J.*, 1936, 1750) in the seed-wax of *Simmondsia californica*, a plant which is peculiar in elaborating waxes (esters of eicosenoic and erucic acids with eicosenyl and docosenyl alcohols) and not glycerides in its seeds. In 1946, Hopkins (*Canadian J. Res.*, 1946, **24**, B, 211) observed that small proportions of the same acid accompanied erucic, linoleic, and oleic acids in the seed oil of hare's ear mustard (*Conringia orientalis*, Cruciferæ), and subsequently we have found that, although previously overlooked, it is similarly present in rape-seed oil and mustard-seed oil (see also p. 248).

Cetoleic acid is a docosenoic acid present in small proportions in most fish fats.

Unsaturated Acids in Fatty Oils from Aquatic Sources.

It was mentioned earlier that polyethenoid acids with four, five, and six double bonds are very prominent in fatty oils from aquatic flora and fauna; these acids appear to be constituted quite differently from any which we have considered up to the present point in this discussion, and also from the monoethenoid fatty acids which occur along with them in fats of aquatic origin.

Monoethenoid Acids of Marine-animal Fats.—To emphasise this point, it is desirable to tabulate (Table VII) the monoethenoid acids so far encountered in marine fats, although these have already appeared in one or other of Tables I, III, and VI. It is apparent from Table VII that no simple relationship, such as those to which attention has been drawn in the preceding tables, seems to be characteristic of the "marine" monoethenoid acids. The grouping $\cdot C\cdot[CH_2]_7\cdot C\cdot$ occurs, however, in all but one of these acids, whilst in the C_{20} and C_{22} members of the series the system $\cdot C\cdot[CH_2]_9\cdot C\cdot$ also appears.

TABLE VII.

Monoethenoid acids of marine-animal fats.

$C_{14}H_{26}O_2$	Tetradec-5-enoic (sperm-head)	$CH_3\cdot[CH_2]_7\cdot CH{:}CH\cdot[CH_2]_3\cdot CO_2H$
$C_{14}H_{26}O_2$	Tetradec-9-enoic (myristoleic)	$CH_3\cdot[CH_2]_3\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$
$C_{16}H_{30}O_2$	Hexadec-9-enoic (palmitoleic)	$CH_3\cdot[CH_2]_5\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$
$C_{18}H_{34}O_2$	Octadec-9-enoic (oleic)	$CH_3\cdot[CH_2]_7\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$
$C_{20}H_{38}O_2$	Eicos-9-enoic (gadoleic)	$CH_3\cdot[CH_2]_9\cdot CH{:}CH\cdot[CH_2]_7\cdot CO_2H$
$C_{22}H_{42}O_2$	Docos-11-enoic (cetoleic)	$CH_3\cdot[CH_2]_9\cdot CH{:}CH\cdot[CH_2]_9\cdot CO_2H$
$C_{24}H_{46}O_2$	Tetracos-15-enoic (selacholeic)	$CH_3\cdot[CH_2]_7\cdot CH{:}CH\cdot[CH_2]_{13}\cdot CO_2H$

Polyethenoid Acids of Marine-animal Fats.—When we turn to the corresponding polyethenoid acids (Table VIII) a completely different type of structure is encountered, in which the only resemblance to other natural polyethenoid acids is the frequent occurrence of the pentadiene system $\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot$. The most striking difference from other natural unsaturated fatty acids is the point (usually Δ^4) at which unsaturation begins, the unsaturated molecules terminating almost invariably in the system $\cdot CH{:}CH\cdot[CH_2]_2\cdot CO_2H$.

TABLE VIII.

Polyethenoid acids of marine-animal fats.

$C_{16}H_{26}O_2$	Hexadecatrienoic (hiragonic)	$\Delta^{4:10:14}$
$C_{16}H_{24}O_2$	Hexadecatetraenoic	$\Delta^{4:8:11:14}$ or $\Delta^{4:9:12:15}$
$C_{18}H_{28}O_2$	Octadecatetraenoic (moroctic)	$\Delta^{4:8:12:15}$
$C_{20}H_{32}O_2$	Eicosatetraenoic (arachidonic)	$\Delta^{4:8:12:16}$
$C_{20}H_{30}O_2$	Eicosapentaenoic	$\Delta^{4:8:12:15:18}$
$C_{22}H_{34}O_2$	Docosapentaenoic (clupanodonic)	$\Delta^{4:7:13:16:19}$ or $\Delta^{4:8:11:15:19}$ or $\Delta^{4:8:12:15:19}$
$C_{22}H_{32}O_2$	Docosahexaenoic (clupanodonic)	$\Delta^{4:8:12:15:18:21}$ or $\Delta^{4:8:11:14:17:20}$
$C_{24}H_{36}O_2$	Tetracosahexaenoic (nisinic)	$\Delta^{4:8:12:15:18:21}$

The structures given in Table VIII are as allocated by Tsujimoto, Toyoma, and other Japanese workers. Farmer and van den Heuvel (*J.*, 1938, 427; *J. Soc. Chem. Ind.*, 1938, **57**, 24) isolated methyl docosahexenoate from the acids of cod-liver oil by use of the molecular still, thereby avoiding risk of isomerisation and polymerisation by exposure to a temperature above 120°; from the scission products obtained by oxidation of the ester they deduced that the acid

contained four :CH·CH$_2$·CH: groups and one :CH·[CH$_2$]$_2$·CH: group between the terminal groups CH$_3$·CH: and :CH·[CH$_2$]$_2$·CO$_2$H. Their docosahexaenoic acid therefore possessed one of the following structures :

$\Delta^{4:8:11:14:17:20}$	CH$_3$·CH[:CH·CH$_2$·CH]$_4$:CH·[CH$_2$]$_2$·CH:CH·[CH$_2$]$_2$·CO$_2$H
$\Delta^{4:7:11:14:17:20}$	CH$_3$·CH[:CH·CH$_2$·CH]$_2$:CH·[CH$_2$]$_2$·CH:CH·CH$_2$·CH:CH·[CH$_2$]$_2$·CO$_2$H
$\Delta^{4:7:10:14:17:20}$	CH$_3$·CH[:CH·CH$_2$·CH]$_2$:CH·[CH$_2$]$_2$·CH[:CH·CH$_2$·CH]$_2$:CH·[CH$_2$]$_2$·CO$_2$H
$\Delta^{4:7:10:13:17:20}$	CH$_3$·CH:CH·CH$_2$·CH:CH·[CH$_2$]$_2$·CH[:CH·CH$_2$·CH]$_2$:CH·[CH$_2$]$_2$·CO$_2$H
$\Delta^{4:7:10:13:16:20}$	CH$_3$·CH:CH·[CH$_2$]$_2$·CH[:CH·CH$_2$·CH]$_3$:CH·[CH$_2$]$_2$·CO$_2$H

Whilst there is general agreement in the above data that unsaturation begins at the Δ^4 position in the fatty acid chain in these polyethenoid acids from marine sources of fat, Dolby, Nunn, and Smedley-MacLean (*Biochem. J.*, 1940, **34**, 1422) and Mowry, Brode, and Brown (*J. Biol. Chem.*, 1942, **142**, 671, 679) concur in finding that the arachidonic acid in animal adrenal phosphatides is eicosa-5 : 8 : 11 : 14-tetraenoic acid. This may indicate that the arachidonic acid of land animals differs from that in marine fats. However this may be, these highly unsaturated acids of natural fats stand quite apart in their constitution from any of the other natural unsaturated fatty acids, and therefore appear to be the result of quite independent synthetic processes from those which determine the production of oleic, hexadecenoic, linoleic, and most other unsaturated acids of natural fats.

Characteristic Unsaturated Acids in the Seed Fats of the Cruciferæ.

In the foregoing discussion nearly all the known natural unsaturated fatty acids have been displayed in groups which reflect well-marked similarities in their structure. It is equally interesting to consider the different types of unsaturation which are found together in fats of related biological origin (as, for instance, the fats from marine fauna which give rise to the complex mixture of unsaturated fatty acids dealt with in the preceding section). Another example which seems worthy of brief reference is the mixture of acids present in seed fats of the family Cruciferæ, both because it exhibits well-marked features peculiar to this family, and because very recent work has added to our knowledge of this group.

The mixture of acids present in these seed fats is peculiarly difficult to determine quantitatively, but a recent analysis of the component acids in a typical rape-seed oil has given the following data, which probably give a good approximate picture of the general nature of these fats :

Saturated acids,%	Palmitic, 2·5; stearic, 1·5; arachidic–behenic–lignoceric, 3.
Unsaturated C_{16} acids,%	Hexadecenoic, 1.
„ C_{18} acids,%	Oleic, 13; linoleic, 16; linolenic, 9.
„ C_{20} acids,%	Eicosenoic, 5.
„ C_{22} acids,%	Erucic, 48; docosadienoic, 1.

The " newcomers " to this group are hexadecenoic (now recognised as a trace constituent of most vegetable seed fats, *cf.* Hilditch and Jasperson, *J. Soc. Chem. Ind.*, 1938, **57**, 84), the eicosenoic acid first observed in hare's ear mustard-seed oil by Hopkins (*loc. cit.*), and the small amount of docosadienoic acid which accompanies the large proportion of erucic acid in these fats and which was first detected by Hilditch, Laurent, and Meara (*J. Soc. Chem. Ind.*, 1947, **66**, 19). Hopkins, in his communication on hare's ear mustard-seed oil, suggested that the eicosenoic acid which he had proved to be present therein might be either absent from other Cruciferæ (*e.g.*, *Brassica*) seed fats, or that its presence in small quantities might have been overlooked. Further work by Baliga in my laboratory shows that the latter explanation is the correct one, and we have now isolated the acid from, and determined its approximate proportion in, several specimens of rape-seed oil.

Again, the facts that ester-fractions of the unsaturated C_{22} acids from an ordinary mustard-seed oil (Hilditch, Laurent, and Meara, *loc. cit.*) showed somewhat higher unsaturation than that due to methyl erucate alone, and that on treatment with alkali at 180° they gave rise to an absorption band at 234 mμ indicative of conjugated diene unsaturation, indicated the presence of small amounts of a docosadienoic acid. We have since confirmed this in a number of rape-seed oils, and have isolated the dienoic acid and determined its constitution, namely, docosa-13 : 16-dienoic acid. These results will be communicated in detail in a future paper, but may be briefly summarised here.

These minor component unsaturated acids are concentrated, during the determination of the total component acids, in the fraction of the total acids which is most soluble in acetone at a low temperature, and which contains nearly all the oleic, linoleic, and linolenic acids, with some

erucic acid, in addition to most of the small amount of hexadecenoic, eicosenoic, and docosadienoic acids present. An example of the ester-fractions obtained on distillation of the methyl esters of typical concentrates of this kind from rape-seed oils is given in Table IX, together with the theoretical equivalents and iodine values of the individual methyl esters which may be present.

TABLE IX.

Typical fractionation data for methyl esters of unsaturated acids from a rape-seed oil.

Fract. No.	Wt., g.	Equiv.	Iodine value.	Ester.	Equiv.	Iodine value.
1	3·5	269·8	66·9	Methyl hexadecenoate	268·0	94·8
2	4·2	289·1	132·4	,, oleate	296·0	85·8
3	6·1	292·4	149·3	,, linoleate	294·0	172·8
4—9	32·9	293·4—294·5	153·6—154·9	,, linolenate	292·0	261·2
10	4·7	294·9	152·5	,, eicosenoate	324·0	78·4
11	4·1	308·2	124·2	,, erucate	352·0	72·2
12	5·1	323·4	92·5	,, docosadienoate	350·0	145·1
13	4·9	327·6	85·6			
14	8·6	349·9	79·8			
15—17	12·6	350·8—355·6	77·0—78·4			

In many earlier fractional distillations of rape-seed oil esters we had often noticed the regular occurrence of small fractions with equivalents in the region of 324 ± 2, but had regarded them as intermediate mixtures between the large bulks of unsaturated C_{18} and C_{22} esters in process of separation. In view of Hopkins's work, however, we accumulated sufficient fractions of this nature for further examination; as expected, they indeed still contained both unsaturated C_{18} and C_{22} esters, but, by refractionation, we eventually obtained specimens, approximating in equivalent and iodine value to those of methyl eicosenoate, which were undoubtedly esters of an eicosenoic acid. Derivatives prepared from this acid, and the scission products obtained by oxidation of its ester, in all respects confirmed Hopkins's conclusion that the acid was eicos-11-enoic acid.

Similar study by Baliga of accumulated fractions of the nature of nos. 14—17 in Table IX, by means of somewhat tedious concentration of the diene acid by low-temperature crystallisation from acetone or ether, eventually led us to an acid with iodine value 130 (calc., 151·2) which was a mixture of about two-thirds of the dienoic acid with one-third of erucic acid. Scission-oxidation of the methyl esters from the concentrate of the acid yielded brassylic and hexoic acids, thus establishing its structure as docosa-13 : 16-dienoic acid. The acid yielded a crystalline tetrabromobehenic acid which melted at 106—107°.

The group of homologous unsaturated fatty acids containing 18, 20, and 22 carbon atoms in rape- and mustard-seed oils (and probably in most other Cruciferæ seed fats) thus presents the interesting relationships shown in Table X. It will be seen at once that in each the unsaturated groups are situated at the end of the molecule remote from the carboxyl group, *i.e.*, they are all structurally derived from the system $CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot$. (The structure of the hexadecenoic acid in rape-seed oil, as in other seed fats, has been found to be the same as that of the acid in fats from other classes of fauna and flora, namely, hexadec-9-enoic acid.)

TABLE X.

Unsaturated C_{18}, C_{20}, and C_{22} acids in Cruciferæ seed fats.

$C_{18}H_{30}O_2$	Linolenic	$CH_3 \cdot CH_2 \cdot CH{:}CH \cdot CH_2 \cdot CH{:}CH \cdot CH_2 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$
$C_{18}H_{32}O_2$	Linoleic	$CH_3 \cdot [CH_2]_4 \cdot CH{:}CH \cdot CH_2 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$
$C_{18}H_{34}O_2$	Oleic	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$
$C_{20}H_{38}O_2$	Eicosenoic	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_9 \cdot CO_2H$
$C_{22}H_{42}O_2$	Erucic	$CH_3 \cdot [CH_2]_7 \cdot CH{:}CH \cdot [CH_2]_{11} \cdot CO_2H$
$C_{22}H_{40}O_2$	Docosadienoic	$CH_3 \cdot [CH_2]_4 \cdot CH{:}CH \cdot CH_2 \cdot CH{:}CH \cdot [CH_2]_{11} \cdot CO_2H$

The Origins of Oleic and Linoleic Glycerides in Seed Fats. Some Facts and a Few Speculations.

One is reluctant to conclude without brief reference to the fascinating topic of biosynthesis of fatty glycerides in the ripening seed. Such reference may be profitably mainly restricted to the experimentally ascertained facts at present available, since these are still insufficient to warrant any attempt at even partial explanation of the chemical processes involved.

That seed fats are built up from pre-formed sugars—probably mainly hexoses—is well established; some data from one of the classical studies of du Sablon (*Rev. gén. Bot.*, 1897, **9**, 313) are reproduced (Table XI) to illustrate this.

TABLE XI.

Carbohydrate and fat contents in almonds during ripening.

	June 9.	July 4.	August 1.	September 1.	October 4.
Glucose, %	6·0	4·2	0	0	0
Sucrose, %	6·7	4·9	2·8	2·6	2·5
Starch, %	21·6	14·1	6·2	5·4	5·3
Fat, %	2·0	10·0	37·0	44·0	46·0

No intermediate products between sugar and fatty acids having yet been isolated, the many attempts which have been made to explain the mechanism involved are largely conjectural. It is perhaps fair to say that, on the whole, it seems likely that initial breakdown of hexose *via* pyruvic acid to an acetaldehyde-like nucleus, followed by condensation of this to give aldol-like rather than polyene aldehyde products, forms the basis of the process. The reasons for, on the one hand, the frequent tendency to form the C_{18} chain, and, on the other hand, the production of chains (notably C_{16}, but also C_{12}, C_{14}, C_{20}, or C_{22} in specific biological groups) of carbon content other than C_{18}, are at present obscure, as also are those for the peculiarly definite groupings in the unsaturated fatty acids which have formed the main topic of this discussion.

Two aspects of the elaboration of seed-fat glycerides are, however, quite clearly established by experimental observation: (*a*) in the early stages of ripening, free fatty acids predominate, and the final fat consisting of neutral triglycerides is only fully developed at a comparatively late stage of maturity, and (*b*) the mean unsaturation of a seed fat (which at maturity is relatively highly unsaturated) usually at first only slightly exceeds that of monoethenoid glycerides, rapid increases in unsaturation occurring at a late stage in the ripening of the seed. These facts were first noted by Ivanow (*Beihefte bot. Zent.*, 1912, **28**, 159) in the ripening seeds of rape, hemp, poppy, and flax, and the final rapid increase in unsaturation is illustrated in Table XI by some figures from subsequent work by Vargas Eyre (*J. Agric. Sci.*, 1915, **7**, 120; *Biochem. J.*, 1931, **25**, 1902) on ripening linseed.

TABLE XI.

Development of fatty oil, and of its unsaturation, in ripening flax seed.

Days after flowering.	Oil (dry seeds), %.	Iodine value.
10	2·5	114
14	15·1	119
17	31·1	127
23	37·0	143
28	36·9	170
35	36·8	180
51	36·3	190

Exactly similar sequences of changes have since been observed during ripening of cottonseed (Caskey and Gallup, *J. Agric. Res.*, 1931, **42**, 671; Lonzinger and Raskina, *Maslob. Shir. Delo*, 1931, Nos. 2—3, 57), niger seed (Sahasrabuddhe, *Indian J. Agric. Sci.*, 1932, **3**, 57), soya bean (Rewald and Riede, *Biochem. Z.*, 1933, **260**, 147), and lupins (Neumann, *ibid.*, 1941, **308**, 141). Clearly, the ultimate production of a mixture of unsaturated fatty acids in which more linoleic acid than oleic acid is present than at earlier stages can arise in one of two ways: (*a*) desaturation of pre-formed oleic glycerides, or (*b*) preferential synthesis in the later stages of linoleic rather than oleic acid. Unfortunately, results so far published are expressed on a percentage basis, whereas an attempt to assess the total amount of these fatty acids produced at different stages (*e.g.*, per 100 or per 1000 fruits) might have enabled this important point to be settled. Perhaps it is permissible to feel, in the absence of direct evidence, that the synthesis from the products of sugar metabolism is more likely to lead to different fatty acids at different stages of seed maturity than that a dehydrogenation of pre-formed oleic acid is involved. It is also perhaps pertinent here to refer to recent work by E. H. Farmer and others which has defined the special characteristics of the pentadiene grouping, $\cdot CH{:}CH\cdot CH_2\cdot CH{:}CH\cdot$, with its central "reactive" methylene group, and to suggest that, just as this system behaves specifically in its reactivity with oxygen or with hydrogen, so also it may on occasion serve as a specific halting point in the biosynthesis of unsaturated fats: it certainly appears with great frequency in these compounds.

A more practical point is that, under different conditions, seeds of a given species may yield fats in which the proportions of oleic and linoleic acid vary somewhat widely. It is possible to illustrate this from the results of many component acid analyses of seed fats, a selection of which is given in Table XII. The causes of the variation are not clearly differentiated, but

the instances given in Table XII show that (*a*) the specific variety of a plant species, (*b*) the climatic (especially temperature and humidity) conditions of growth, and (*c*) the nature of the soil and probably other factors can all influence the composition of the seed fat.

TABLE XII.*

Variation in oleic and linoleic acid contents of some seed oils from different sources.

	Iodine value.	Component acids, %.			
		Satd.	Oleic.	Linoleic.	Linolenic.
Groundnut oil (Leguminosæ):					
India	93	23	46	31	—
Nigeria	86	19	61	20	—
Argentina	100	25	42	33	—
Soya bean oil (Leguminosæ):					
" Dunfield " var., Missouri 1936	103	12	59	28	1
" " " 1937	124	13	33	51	3
" Indiana 1937	127	13	31	53	3
Linseed oil (Linaceæ):					
" Bison " var., Minnesota	163	11	30	18	40
" Saskatchewan	187	9	22	15	54
" Redwing " var., Minnesota	182	10	23	15	52
" Saskatchewan	195	8	16	18	57
Niger-seed oil (Compositæ):					
West Africa	136	12	16	72	—
India	129	9	39	52	—
Safflower-seed oil (Compositæ):					
Carthamus tinctorius, U.S.A.	149	7	26	67	—
" India	136	6	33	61	—
C. oxyacantha, India	112	7	56	37	—
Sunflower-seed oil (Compositæ):					
Europe	136	11	22	67	—
U.S.A.	131	7	34	59	—
India	112	10	49	41	—

* The data in Table XII are due to the following authors: soya bean oils, Dollear, Krauczunas, and Markley (*Oil and Soap*, 1938, **15**, 263); linseed oils, Painter and Nesbitt (*ibid.*, 1943, **20**, 208); niger seed oil (India), Vidyarthi and Mallya (*J. Indian Chem. Soc.*, 1940, **17**, 87); safflower (India, *C. tinctorius*), Vidyarthi (*ibid.*, 1943, **20**, 45); (U.S.A.) Jamieson and Gertler (*Oil and Fat Ind.*, 1929, **6**, No. 4, 11); sunflower (U.S.A.), Baughman and Jamieson (*J. Amer. Chem. Soc.*, 1922, **44**, 2952); sunflower and *C. oxyacantha* (India), Kumar (Thesis, University of Allahabad, 1947). The figures for the groundnut oils, niger-seed (West Africa), and sunflower seed (Europe) oils are from work in the Department of Industrial Chemistry, University of Liverpool.

Variations due to botanical variety may possibly operate in the group of groundnut oils, and almost certainly do so in the two nearly-related species of *Carthamus* (Indian safflower-seed oils); the clearest illustration of this influence in Table XII is, however, the different composition of oils from " Bison " and " Redwing " varieties of *Linum usitatissimum* when grown in the same locality (*e.g.*, Minnesota).

It has become recognised that seed of the same variety grown in climates in which the mean temperature is markedly different yields a more unsaturated fatty oil in the colder regions; this is well illustrated by the increased linolenic and diminished oleic acid contents of the two varieties of linseed grown in Saskatchewan as contrasted with those from Minnesota. Temperature is not, however, the only factor involved: thus the " Dunfield " variety of soya bean grown in Missouri in two successive seasons yielded oils widely different in their oleic and linoleic contents. In 1936 the season was not only abnormally hot but also abnormally dry, and the unusually low unsaturation of the oil from the 1936 crop is attributed by Dollear *et al.* (*loc. cit.*) to other environmental factors as well as to temperature.

The data for the three *Compositæ* seed fats in Table XII emphasise these points in three oils which have some technical interest as " drying oils ", thus suggesting that the choice of site and cultivation of such crops must be carefully considered from the standpoint of the component acids produced in the seed oils. The Indian sunflower-seed oil quoted is exceptionally interesting in this respect, since Kumar states that the seed was of known origin—a strain originally brought from Russia to the United States, where it was grown for four generations (which there yielded typical American oil of higher linoleic and lower oleic content) before seed from the fourth generation was used in India and furnished oil with only 41% of linoleic acid in its component acids.

In conclusion, attention may be directed to the importance of detailed analyses of the unsaturated acids in oils thus grown for technical purposes, and also to the possibility of undertaking further studies of the development of the fatty components as the seeds ripen, in order to obtain much needed further information as to what takes place. In the United States, work of this kind is being undertaken at research centres within reach of the crops, and it should be stressed that such studies should be carried on near the areas of cultivation of the oilseed crops. It appears important that, where large-scale cultivation of different oil-bearing seeds is contemplated or in progress in tropical or sub-tropical parts of the British Commonwealth, local research stations should not only be concerned with the cultivation problems immediately involved, but should include one or more chemists skilled in the modern techniques of component fatty acid and mixed glyceride determinations, and have facilities to make use of them. Progress can only be slow and uncertain if specimens of oil have to be sent to this country for study, and in the investigation of fat production at progressive stages of the ripening seed it is useless to expect much progress until the experimental chemical work can be carried on close to where the seed is being grown. Since such studies would undoubtedly contribute largely to fundamental knowledge of fatty synthesis in the plant and of the manner in which the many different natural fatty acids—saturated as well as unsaturated—may arise, it is not inappropriate to conclude this lecture by a reference to this important practical point.

OBITUARY NOTICES.

GEORGE THOMAS BYRNE.

1885—1944.

NEWS has recently been received of the death of Professor G. T. Byrne while a prisoner in Japanese hands.

George Thomas Byrne was born in Blackburn on June 2nd, 1885. He was educated at the Higher Grade School, Blackburn, and at Manchester University, where he graduated in 1908 with first class honours in chemistry. For the next two years he was private research assistant to Dr. (now Sir Robert) Pickard at Blackburn Technical College. His assistance to Pickard and Kenyon in some of their early work on the resolution of secondary alcohols is referred to in the *Proceedings* (1912, **28**, 42).

In 1910 he began his long career in academic posts overseas. His first post was a science master at St. Mary's School, Cairo. In 1914 he moved to Jamaica as science master first at Wolmer's School and later at Munro College. In 1919 he was appointed Professor of Chemistry at the University of Hong Kong, and this began an association which was to last for 25 years. He became an M.Sc. of Manchester in 1911, A.R.I.C. in 1923, and F.R.I.C. in 1930.

Byrne returned to England in 1929—1930 with a long period of leave and joined Sir Jocelyn Thorpe's research school at the Imperial College. The writer had at that time just begun to investigate the phthalocyanines, and Byrne was his first research collaborator in that field. I have a vivid recollection of Byrne in those highly pigmented days. His laboratory coat became steadily more green and blue, the more immersed he became in the subject. His particular contribution was the early investigation of the formation of phthalocyanines from the interaction of metals (and their derivatives) with the dehydration products of phthalamide and particularly with *o*-cyanobenzamide. This provided the first controlled method for the preparation of metallic phthalocyanines. Byrne pursued this work with relish and a refusal to be daunted by the many peculiarities of the new materials. The results were published in 1934 (*J.*, 1017).

Byrne returned to Hong Kong in 1930. The regard in which he was held is shown by his appointment as Dean of the Faculty of Arts in 1932 (a post he had previously held in 1925); as representative of the University at the Congress of the Universities of the British Empire in Edinburgh in 1931; and as Member of the University Council in 1937.

Byrne had a gentle and kindly nature. He was a very popular member of the Hong Kong staff, and will long be remembered by his students for his conscientious devotion to his department.

His life closed in an atmosphere of violence in sad contrast to the long period of quiet valuable service which had gone before. On Christmas Day, 1941, following the capture of Hong Kong, Byrne was interned by the Japanese. At first he was confined in the University grounds, but later he was transferred to the Civilian Internment Camp at Stanley. There he died on June 1st, 1944, from heart failure, while grinding rice.

I am indebted to Sir Robert Pickard, to the Registrar of the University of Hong Kong, and to the Secretary of the Royal Institute of Chemistry for biographical information.

R. P. LINSTEAD.

DAVID HOOPER.

1858—1947.

DAVID HOOPER was born at Redhill, Surrey, in 1858 and was educated at Chelmsford, to which town his parents moved shortly after his birth. In 1887 he married Miss Hannah Carr Evans, a daughter of the Reverend Thomas Evans, a Baptist minister of Mussoorie, U.P., India, who survives him with three daughters. His two sons pre-deceased him, the elder being killed on active service in France in 1915. Hooper died on January 31st, 1947, at Bromley, Kent, and was buried in Islington Cemetery.

In 1878 Hooper was awarded the Herbarium Bronze Medal presented annually by the Pharmaceutical Society of Great Britain for the best herbarium collected during the year by a pharmaceutical apprentice. This early interest in plants remained with him to the end of

his long life, and, though he regarded himself as a chemist, he might with equal accuracy have been described as an economic botanist. In 1880, as a student at the Pharmaceutical Society's School, he qualified as a pharmaceutical chemist and distinguished himself by winning the Pereira Medal, the highest award the Society can offer to a pharmaceutical student. He then spent three years in the laboratories of pharmaceutical firms in London, gaining experience in the analysis of natural drugs, which was of great value to him in his later career. In 1884 he was appointed quinologist to the Government of Madras, and spent six months in Holland studying records of cinchona planting in Java and Dutch methods of quinine manufacture, before proceeding to Ootacamund, Madras, to take up his official appointment, which he retained until 1896. The first half of the latter year he was Officiating Government Botanist and Director of Cinchona Plantations in Madras, and in the second half he did duty as Officiating Reporter on Economic Products to the Government of India, a post he held again in 1898—99 and 1905. In 1902 he was also for a time Officiating Government Chemist. His own post during this period, 1897—1914, was that of Curator of the Economic and Art Section of the Indian Museum, and the fact that he was so frequently seconded to act for scientific colleagues is a tribute to his versatility and his profound knowledge of plants and their constituents. On his retirement in 1914 he returned to England, and during the first World War was engaged in supervising chemical work under the Ministry of Munitions. After 1919 he worked for a time in the biochemical laboratory at Bristol University. His last important task was the botanical investigation of native drugs and plants from South-Western Asia. The material studied included three collections, one made by Drs. Cowan and Darlington in 1929 (*Kew Bulletin*, 1930, pp. 49—68), a second in 1929 and subsequent years by Captain P. Johnston-Saint of the Wellcome Historical Medical Museum, and a third by Mr. Henry Field, leader of the Field Museum Anthropological Expedition to the Near East in 1934. The results of this study were published by Hooper, Field, and Dahlgren as " Useful Plants and Drugs of Iran and Iraq " (*Field Museum of Natural History, Botanical Series*, 1937, No. 3, pp. 71—241). No new drugs or plants were found, but, like most of Hooper's papers, this one illustrates his flair for eliciting curious, interesting, and suggestive information.

Though Hooper was a prolific writer he published comparatively little original laboratory work, and that was mainly of an analytical type on the constituents of plants alleged to be of therapeutic value or to serve some other useful purpose. There are many papers arising out of his work as a quinologist, including in 1884 a series of analyses of cinchona barks of historical interest, a favourable commentary on the polarimetric method for the analysis of commercial quinine sulphate—a subject on which there was at the time (1886) much discussion among quinologists—and a review of cinchona cultivation in Java from 1872 to 1907. Several papers deal with the work and problems of a quinologist in the Madras Cinchona Plantations and discuss the yields of alkaloid from different species of *Cinchona* and their hybrids, and the effects on yield of age and of variation in conditions of cultivation and harvesting. These papers contain the results of hundreds of analyses of cinchona bark and bear tribute to the industry and scientific enthusiasm of the young quinologist. Mention may also be made of his isolation of the alkaloid vasicine from *Adhatoda vasica*. It was subsequently found by the late Professor Späth in *Peganum harmala* and shown to be of a new type based on a quinazoline nucleus.

Hooper's chief service to science lies in his industrious and meticulously careful collection, arrangement, and publication of information regarding the origin, composition, and uses of plants, especially drugs. He published many notes and papers on such subjects in the *Pharmaceutical Journal*, the *Agricultural Ledger of India*, and the *Journal of the Asiatic Society of Bengal*. His most important work of this kind is his share in " Pharmacographia Indica," a three-volume work prepared in association with two Indian Army surgeons, Drs. Dymock and Warden. Each Indian drug is the subject of an erudite monograph, which includes original medical or chemical observations by the authors. So little chemical work has been done on the constituents of plants that this book published 55 years ago is still useful as a guide in the selection of plant material for chemical investigation. It contains, for example, useful information on *Dichroa febrifuga*, *Dæmia extensa*, *Alangium Lamarckii*, and other plants which have recently been the subject of chemical investigation, as part of what seems to be a minor revival of interest among chemists in the constituents of plants.

Hooper's work was recognised by the award to him of the Hanbury Gold Medal in 1907, of which two previous recipients, Sir George Watt and Dr. Dymock, were his associates in India. In 1914 he was given the honorary degree of LL.D. by the McMaster University of Toronto, and in 1916 he was President of the British Pharmaceutical Conference. He joined

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